Chapter 95

Acute Treatment of Cluster Headaches

Giorgio Sandrini and Thomas N. Ward

The pain of cluster headache is often described as the most severe of any known pain. Because the pain is maximal at or near onset (within 15 minutes), yet lasts less than 3 hours (often about 45 minutes), acute therapies need to work rapidly and ideally be self-administered. Parenteral routes of administration are preferred to achieve reliable and fast pain relief (42).

Additionally, because the cluster attacks can occur multiple times daily, there is legitimate concern about potential cumulative drug toxicity, tolerance, and potential addiction. Coexistent medical conditions, such as coronary artery disease, which is common in this patient population, present significant therapeutic limitations. Fortunately, there are numerous effective options to abort cluster attacks, and some patients may benefit from having more than one choice. These options must be selected keeping in mind whatever prophylactic medications the patient has been given to avoid adverse drug interactions and side effects.

Acute therapy for cluster headaches includes oxygen inhalation, ergots, triptans (especially sumatriptan subcutaneous injection), analgesics, intranasal local anesthetics, and other less familiar agents. Criteria for choosing among these treatments should include ease of administration (ideally self-administered) and speed of relief (ideally within 15 minutes). Some older remedies are vanishing from the therapeutic armamentarium, but are still of historical interest.

ERGOTS

Ergots were the earliest effective therapy, although they have been largely supplanted by newer agents (3). Horton demonstrated that intravenous ergotamine tartrate 0.2 to 0.3 mg rapidly terminated attacks of cluster headache (15). Horton and others also studied the use of ergotamine tartrate 1 mg and caffeine 100 mg (17). Two tablets at attack onset was the effective dose. Unfortunately, the oral route of administration does not work rapidly or reliably enough. Taking this drug sublingually or by inhalation can be highly effective, when available (20,40). Suppositories of ergotamine and caffeine have been utilized, but again are generally not fast enough, although some have used oral and rectal ergotamine as prophylaxis (36).

Dihydroergotamine mesylate 0.5 to 1 mg intravenously, preceded by 10 mg metoclopramide intravenously rapidly terminates attacks of cluster headache. Benefit occurs in less than 15 minutes (26). This strategy is most appropriate for the office or emergency room. Dihydroergotamine may also be self-administered subcutaneously or intramuscularly at 1 mg two to three times daily, although these routes do not provide relief as quickly. Intranasal dihydroergotamine as reported does not work fast enough to shorten individual attacks, but may lessen their severity (1). The optimal dose by this route is unclear and 2 mg administered intranasally might be effective (39). Personal observations on the use of a compounded 2 mg suppository suggest too slow an onset of action to be a therapeutic consideration given the variety of options available (43).

Ergots have effects at many receptors, including 5-$HT_{1D/1B}$. They are known to suppress neurogenic inflammation and prevent the release of inflammatory neuropeptides, including CGRP (24). The side effects of ergots are well known and limit their usefulness in treating cluster headache. They are vasoconstrictors and therefore should be avoided in patients with coronary artery disease, vasospastic angina, Raynaud disease, and other vascular diseases. They are also contraindicated in uncontrolled hypertension and pregnancy. Concomitant use with other vasoconstrictors such as methysergide and triptans should be avoided. Limitations on ergotamine dosing to 6 mg per day and 10 mg per week have been advocated to avoid ergotism, although other parameters are sometimes utilized (36). There are also limitations on dihydroergotamine use ($\leq$3 mg per day), although this drug may be better tolerated. Nausea can be treated with antiemetics, and leg

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cramps respond to dose reduction. Diarrhea usually responds to diphenoxylate and atropine, or loperamide.

OXYGEN

Inhalation of oxygen as a cluster treatment has a number of desirable features. Unlike ergotamine, it is not contraindicated in the presence of coronary artery disease. When used correctly, it is rapidly effective, and can be administered multiple times a day. Like ergotamine tartrate, its use in this condition was first advocated by Horton at the Mayo Clinic (16). Kudrow reported that when used properly, between 70% and 80% of patients respond within 15 minutes, making it an ideal therapy (21). The efficacy of inhaled oxygen has been confirmed in a double-blind study (9). The mechanism of action is unclear. Oxidation of nitric oxide, the putative final common mediator of "vascular" headache is one possibility, resulting in vasoconstriction. Oxygen may suppress neurogenic inflammation. Ultimately, why oxygen is effective is not known (18). Hyperbaric oxygen therapy has been studied in cluster headaches both as acute therapy and as a preventive agent (5,31). At present, the results are contradictory. Benefit may actually be a result of either the hyperbaric condition or a significant placebo effect (32). In any event, it does not seem to offer any advantage over routine oxygen treatment (see below). Even if it were shown to be effective, the lack of hyperbaric chambers and the amount of time required to perform such treatments make them of theoretical interest only.

Many patients use more than one type of oxygen tank, typically a larger tank at the bedside for nocturnal attacks, and a smaller portable tank to take in their car and for the office. During a headache, 100% oxygen at at least 7 L/min by face mask is inhaled. The patient should sit upright, lean slightly forward, and breathe deeply, but not rapidly. Most patients respond well, although some report oxygen use merely delays the headache attack, rather than eradicating it.

TABLE 95-1 Oxygen for Cluster Headaches

100% Fio_2 by mask at 7–10 L/min	Rapidly effective in 70–80% of patients
100% $Fio_2$by mask at 15 L/min	May be effective in those not responding to lower rates (e.g., chronic smokers)
Hyperbaric oxygen	Controversial; experimental at present, but of theoretical interest

A recent report suggests that high-flow oxygen therapy (15 L/min) may be effective in those unresponsive to lower flow rates (35) (Table 95-1).

TRIPTANS

The introduction of sumatriptan to the market was a real revolution in cluster headache treatment, and subcutaneous sumatriptan 6 mg can currently be considered the most effective drug for the management of the cluster headache attack.

The clinical response to subcutaneous sumatriptan appears to be greater and more rapid in cluster headache compared with migraine patients, and the drug is also better tolerated in cluster headache.

Headache relief was obtained in 96% of cluster headache cases at 15 minutes (7,8). The efficacy of subcutaneous sumatriptan was reported to be approximately 8% less in patients with chronic as opposed to episodic cluster headache (12). Given the short duration and severity of the attacks, rapidity of action is a crucial factor. Subcutaneous sumatriptan usually takes effect in 10 to 15 minutes (8) (Fig. 95-1). Increasing the dose from 6 to 12 mg neither increases the number of responders, nor enhances the drug's effect (7). Experience of long-term treatment with sumatriptan is fairly limited in cluster headache, and no evidence of tachyphylaxis has been reported (12) (Fig. 95-2).

Whereas preliminary studies have indicated that sumatriptan is effective in the short-term prophylaxis of menstrual migraine (30), sumatriptan 100 mg orally three

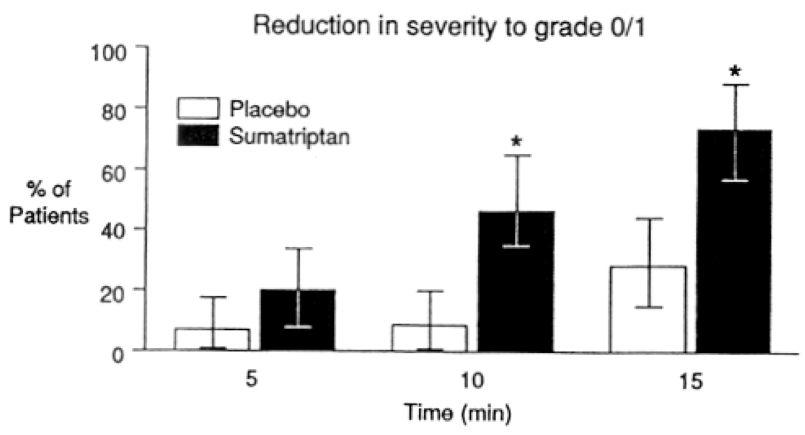

FIGURE 95-1. Response of cluster headache ($n = 39$) to treatment with sumatriptan 6 mg subcutaneously (90). The reduction in the mean score for the severity of headache was significantly larger after the injection of sumatriptan than after placebo at both 10 and 15 minutes.

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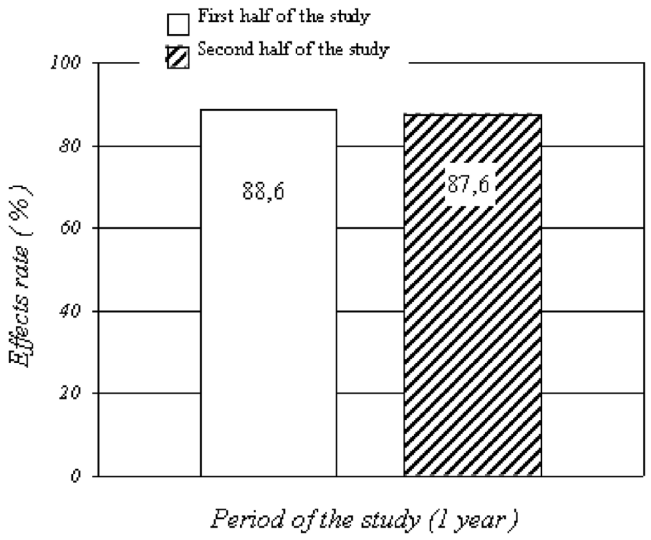

FIGURE 95-2. Long-term efficacy of sumatriptan in 1-year study. Efficacy rates from first half of the study compared with second half does not evidence any significant variation. (Data from [12]).

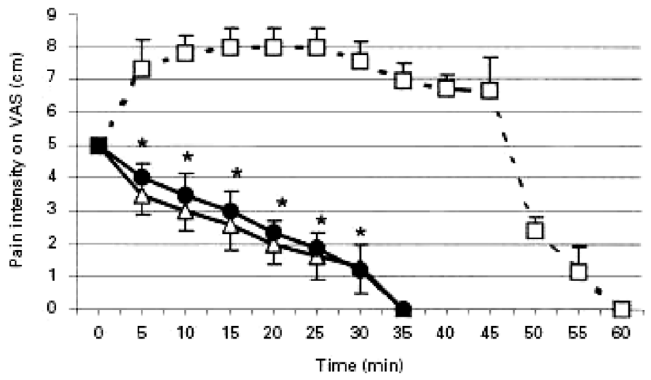

FIGURE 95-3. Mean ± SD values of intensity of NTG-induced pain (VAS) in nine CH patients treated with intranasal cocaine, lidocaine, or saline. **P* < 0.001, both drugs versus saline, Mann-Whitney *U*-test. <hs> saline; <sc> cocaine; <ht> lidocaine. (Reprinted from [4]).

times daily does not alter either the timing or the frequency of cluster headache attacks (28). On the contrary, two case reports have been published in which the prophylactic use of naratriptan, which has a long life, completely prevented the onset of cluster attacks (6,23). Following initial trials of subcutaneous sumatriptan, other routes of administration were investigated, but seem to give poor results. In an open study, sumatriptan nasal spray showed a moderate effect (13,37,41).

Patients with episodic, but not chronic, cluster headache respond to zolmitriptan 5 mg orally (2), which shows moderate efficacy, nevertheless better than placebo.

The triptans show good safety and tolerability (29), but it is important to realize that some patients in clinical practice use more doses daily than indicated on the label. Caution must be exercised above all in the treatment of middle-aged male cluster headache patients, who often present risk factors for cardiovascular disease; tobacco abuse is present in 88% of cluster headache patients (25). The presence of contraindications to triptan use, in particular cardiac ischaemic disease and uncontrolled hypertension, needs to be carefully evaluated.

TOPICAL LOCAL ANESTHETICS

Intranasal anesthesia at the sphenopalatine fossa region level has been tried using several substances. The drug most commonly used is lidocaine (administered by nasal spray, nasal drops, cotton swab). The spray is the easiest method of administration, but gives poor results (22).

Recently, nine patients in a double-blind placebo-controlled study of nitroglycerin-induced cluster headache attack were reported to respond to intranasal lidocaine (Fig. 95-3), with complete cessation of pain within 37.0 ± 7.8 minutes (4), a mean time unacceptable for the majority of patients.

Moreover, the procedure included anterior rhinoscopy, which is not readily available in clinical practice. Similar results were obtained using cocaine, which was faster acting as regards producing complete cessation of the pain (31.3 ± 13 minutes) (22) (see Fig. 95-3). However, the addictive potential and the method of administration limit the usefulness of this drug.

Other open-label trials have explored the effectiveness of intranasal lidocaine (14,19,33). Most patients report results ranging from mild or moderate to poor, and it has been suggested that intranasal lidocaine may be useful only as a possible adjuvant to other abortive treatments in selected cases (25).

ANALGESICS

In spite of the fact that cluster headache patients frequently use analgesics, literature evidence of their effectiveness in this condition is poor. In one study, only 21% of 60 patients reported significant relief of pain with oral analgesics, yet 65% continued using them in spite of their lack of effectiveness (10). Slow absorption, toxicity, and risk of habituation and dependence in prolonged treatments are all factors that argue against the use of oral analgesics in cluster headache.

OTHER DRUGS

The literature also contains preliminary evidence (mainly case reports and open studies) regarding other drugs potentially useful in the treatment of cluster headache attacks.

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Olanzapine, at doses ranging from 2.5 to 10 mg, reduced pain severity by at least 80% within 20 minutes in four out of five cluster headache patients (four chronic and one episodic) (34).

Intravenous verapamil (5 to 7 mg), administered at peak pain during a nitroglycerin-induced cluster headache, resulted in a sudden reduction of pain in part of a group of 15 chronic cluster headache patients (25).

Preliminary studies using intravenous (34) or subcutaneous somatostatin (11) indicate that it could have an efficacy significantly higher than placebo and comparable with that of intramuscular ergotamine, even though it appears less effective at reducing pain duration.

Intravenous magnesium sulphate administration was reported to produce a clinically significant effect in 4% of cluster headache patients with low ionized magnesium levels (27). Data from patients with normal magnesium levels and/or from a placebo-controlled study are not available.

CONCLUSIONS

In spite of the clinical importance of acute treatment of the cluster headache attack, relatively few drugs are available for it. Table 95-2 lists substances that are available. Subcutaneous sumatriptan is the most effective drug, but possible contraindications need to be carefully excluded. Some drugs appear promising, but their effectiveness still needs to be confirmed in controlled studies.

For a fast effect and good availability in clinical practice, the best route of administration seems to be subcutaneous self-injection.

TABLE 95-2 Drugs for Cluster Headache Attack Treatment

Drug	*Comments*
First choice	
Sumatriptan (subcutaneous)	Highest efficacy
Second choice	
Sumatriptan nasal	Less effective than subcutaneous sumatriptan
Zolmitriptan oral	Less effective than subcutaneous sumatriptan
Oxygen	See Table 95-1
Ergotamine (several routes of administration)	Variable efficacy, risk of toxicity in prolonged treatment
Dihydroergotamine (intravenous, intramuscular)	High efficacy, difficult self-administration
Third choice	
Intranasal lidocaine	Mild to moderate relief, slow effect, difficult procedure
Intranasal cocaine	As for lidocaine, risk of addiction
Analgesics	Low efficacy, toxicity
Other, nonvalidated drugs	
Olanzapine	
Somatostatin	
Verapamil	
Magnesium sulfate	

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