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The Clinical Profile of Sumatriptan: Cluster Headache

Key Words

Sumatriptan
Cluster headache
Clinical trials
Migraine

Abstract

Cluster headache is a rare form of severe idiopathic headache characterized by unilateral short-lasting episodes of excruciating pain in association with autonomic disturbances. Subcutaneous sumatriptan has been investigated as an acute treatment for cluster headache in two randomized, double-blind, placebo-controlled, crossover trials. About 75% of patients given subcutaneous sumatriptan 6 mg reported headache relief within 15 min, in comparison with 26-35% given placebo (p < 0.001 in both studies). The need for rescue medication (100% oxygen by inhalation) at 15 min was significantly lower after sumatriptan treatment as were the severity of functional disability and incidence of non-headache symptoms. Results of a long-term study indicate that the tolerability and efficacy of sumatriptan 6 mg is maintained in long-term use, and that there is no evidence of tachyphylaxis.

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Introduction

Cluster headache is a rare, but severe, disorder that has been described in the literature under various names. The earliest known description appeared in Gerhard van Swieten’s medical textbook in 1745 and has recently been translated and published [1]:

‘A healthy robust man of middle age [was suffering from] troublesome pain which came on every day at the same hour at the same spot above the orbit of the left eye, where the nerve emerges from the opening of the frontal bone: after a short time the left eye began to redden, and to overflow with tears; then he felt as if his eye was slowly forced out of its orbit with so much pain, that he nearly went mad. After a few hours all these evils ceased, and nothing in the eye appeared at all changed.’

This early description fulfils the International Headache Society IHS [2] criteria for cluster headache. Before the term ‘cluster headache’ was widely recognized, the disease was known by a variety of names, including histaminic cephalalgia, sphenopalatine, petrosal or migrainous neuralgia, hemicrania periodic neuralgiformis, erythroprosopalgia of Bing and Horton’s headache. Perhaps the least useful name was that given by Sir Charles Symonds who called the condition ‘a particular variety of headache’.

Characteristics and Diagnosis

Cluster headache is characterized by intermittent, repeated, brief attacks of excruciatingly painful unilateral headaches. The pain almost always occurs over the same orbito-temporal region and is associated with autonomic symptoms such as lacrimation, nasal congestion, conjunctival injection or Horner’s syndrome [2], The attacks last between 15 min and 3 h, and their frequency ranges between one every other day to up to eight a day. Most

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cases of cluster headache are episodic, occurring in a series – cluster periods – that may last for several weeks or months, but about 10% of patients experience chronic symptoms. Chronic cluster headache is characterized by cluster periods that last for more than a year without remission, or with remissions of less than 14 days’ duration during any 1 year.

Important differential diagnoses include Tolosa-Hunt syndrome, meningioma of the lesser wing of the sphenoid, temporal arteritis, and head injury with about 16% of sufferers reporting the onset of cluster headache following head trauma. There are some syndromes that share features with cluster headache including chronic paroxysmal hemicrania [2], episodic paroxysmal hemicrania, cluster migraine with a combination of the two syndromes and the so-called SUNCT syndrome characterized by ‘Short-lasting Unilateral Neuralgiform headache with Conjunctival Oedema and Tearing’.

Epidemiology

Cluster headache has been estimated to affect less than 1 % of the population [3], with a higher prevalence in men than in women. Its onset is most frequently between 20 and 40 years of age, but it can occur much later: about 10% of sufferers are in their 60s when they develop the condition. Most sufferers report one or two cluster bouts per year, with one or two headaches per day during bouts. The median duration of bouts is 4-8 months.

Pathogenesis

A number of theories for the pathogenesis of cluster headache have been proposed [3]. Extracranial vascular dilatation occurs during attacks but cerebral blood flow studies have not shown an association between intracranial vascular activity and cluster headaches [4]. It has been proposed that there is a link between attacks and the circadian rhythms of the body. Evidence to support this view comes from observations that there appears to be a relationship between the frequency of cluster headache attacks and changes in the number of daylight hours throughout the year [5], and that the headaches recur at about the same time each day. Since the circadian rhythms of the body are believed to be controlled by the hypothalamus, it is possible that cluster headaches are related to hypothalamic dysfunction. Recently it has also been suggested that the desaturation of oxyhaemoglobin may be involved in the pathogenesis of cluster headaches [6, 7].

The neurotransmitter serotonin (5-HT) may have a role in the pathophysiology of the condition either through a direct vascular effect or through neural mechanisms. In our clinic, we have studied neurological effects in cluster headache. Markers for various nerve systems were monitored in blood taken from the external jugular veins (ipsilateral to the pain) during acute spontaneous attacks and between headache attacks. The markers studied were substance P and calcitonin gene-related peptide (CGRP), both markers of the trigeminal system; vasoactive intestinal polypeptide (VIP) as a marker of the parasympathetic system, and neuropeptide Y as a marker of sympathetic cranial innervation. During the cluster headache attack there were no significant changes in levels of neuropeptide Y or substance P. However, during headache the level of CGRP was elevated about three-fold (p < 0.05) and there was a significant elevation in VIP (p < 0.05) [8]. Similar investigations in migraine sufferers revealed elevations in CGRP levels, but not in VIP, during attacks [9]. It has been proposed that the cranial vessels and their trigeminal innervation form the trigeminovascular system, which has a role both in normal physiology and in migraine [9, 10]. The nerves activated during cluster headache intersect on the carotid artery and, therefore, the role of the trigeminovascular system in cluster headache may be closely related to that proposed for migraine [9], and involve the release of vasodilator neuropeptides and increases in local cerebral blood flow. The mechanisms that trigger the activation of the trigeminovascular system are not yet understood.

Comparison with Migraine

Although migraine and cluster headache have common features, there are a number of differences that aid diagnosis (table 1). Unilateral headache occurs in virtually all cases of cluster headache, but only in about two-thirds of migraine patients. Cluster headaches are of shorter duration than migraine headaches and are less often associated with symptoms such as nausea or photophobia. One marked difference is the response to movement: in migraine patients, the headache is exacerbated by movement, while during a cluster headache attack the sufferers generally move about and rub their heads as they attempt to alleviate the pain.

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Table 1. The clinical features of cluster headache: a comparison with migraine

Clinical feature	
Cluster headache	
Migraine	
Gender ratio (M:F)	
Unilateral pain	
Duration	
Associated with nausea and/or photophobia	
Exacerbation with movement	
Family history	
Visual aura	
Associated with lacrimation, rhinorrhoea, ptosis	
90:10	25:75
~ 100%	66%
15-180min	4-72h
Occasionally	Frequently
No	Yes

No

No

Very often

Often

Sometimes

Very occasionally

The prevalence of migraine is greater in those who have a family history of the disease; it is not believed that there is such an effect in cluster headache, but only limited epidemiological data on the condition are currently available.

Although migraine, particularly in its severe form, causes significant disability [11], the effects of bouts of cluster headache are more extreme. The excruciating pain experienced is extremely disabling and the condition severely affects the patient’s quality of life.

Management of Cluster Headache

Prophylactic therapy is effective in some patients but must be started early in a cluster period [3] and efficacy is often limited by side-effects. The drugs reported to be useful include corticosteroids, verapamil, lithium carbonate, chlorpromazine, ergotamine tartrate, indomethacin, valproic acid and methysergide.

Methysergide is effective, particularly for terminating bouts of headache, but its use can be limited by side-effects which include nausea and vomiting, abdominal discomfort, dizziness or drowsiness. Retroperitoneal, pleural and cardiac valve fibroses have been reported after prolonged dosing [12]. Oral ergotamine is effective, especially in the prevention of nocturnal attacks [3], but this drug also has a well-known side-effect profile, and there is a danger of dependency [13]. Lithium carbonate has been reported to prevent attacks in 40% of patients and is particularly useful in older patients [14]. The calcium channel blocker, verapamil, is also effective in some patients. Since maximal pain intensity is reached very rapidly in attacks of cluster headache, to be effective an acute therapy must give pain relief within a few minutes of administration. Consequently, drugs such as ergotamine or analgesics which can be effective against migraine are of limited use for cluster headache when given orally, although parenteral dihydroergotamine preparations can be successfully used in some patients [3]. The efficacy of inhalation of 100% oxygen in aborting an attack has been demonstrated in controlled trials [15, 16]: the oxygen is administered at 7-10 l/min for up to 15 min. Lignocaine nasal drops (4-6% lignocaine), administered to the nostril ipsilateral to the pain, can also be effective.

Since migraine and cluster headache have some clinical similarities, the novel anti-migraine drug sumatriptan was assessed for efficacy in the acute treatment of cluster headache. The subcutaneous formulation of sumatriptan has been found to provide rapid relief from the pain of cluster headache in a high proportion of patients [17, 18].

Sumatriptan for the Acute Treatment of Cluster Headache

In view of the similarities between migraine and cluster headache, a pilot study was conducted to evaluate whether subcutaneous sumatriptan was of benefit. Following success in this study, a series of larger studies have been undertaken.

In most respects the design of the first study was identical to that used to assess the efficacy of sumatriptan in the acute treatment of migraine; randomized, double-blind, and placebo-controlled. However, because of the rarity of cluster headache a crossover, rather than a parallel-group, design was used [19]. The response to sumatriptan was recorded using a headache severity rating scale similar to that applied in the migraine trials but because of the intensity of the pain experienced during cluster headache attacks, an additional fifth grade for very severe pain was included. Headache relief was defined as an improvement from very severe, severe or moderate headache to mild or absent headache.

Fig. 1. Percentage of patients with cluster headache reporting headache relief, headache free or use of oxygen as rescue medication within 15 min of treatment with subcutaneous sumatriptan 6 mg or placebo. Headache relief defined as a reduction in headache severity from very severe, severe or moderate (severity grades 4, 3 or 2) to mild or none (severity grades 1 or 0). Headache free defined as reduction to severity grade 0. *** p < 0.001 vs. placebo, n = 39. Reprinted with permission from [18].

Fig. 2. Headache relief within 15 min in patients with cluster headache treated with subcutaneous sumatriptan 6 mg, subcutaneous sumatriptan 12 mg or placebo. Headache relief defined as a reduction in headache severity from very severe, severe or moderate (severity grades 4, 3 or 2) to mild or none (severity grades 1 or 0). n = 88 (placebo or sumatriptan 12 mg), n = 92 (sumatriptan 6 mg). *** p < 0.001 vs. placebo for percentage of patients with headache relief and percentage headache-free. Reprinted with permission from Ekbohm et al. [21].

The patients enrolled in the study were admitted to hospital on starting a cluster period and received, in random order, subcutaneous sumatriptan 6 mg for one attack and placebo for the other attack. Thirty-nine patients were evaluable for assessment of efficacy. Sumatriptan was significantly more effective than placebo in relieving headache severity (fig. 1). Within 10 min of injection with sumatriptan 49% of the patients reported headache relief and at 15 min this response had increased to 74%; significantly more patients were headache-free after sumatriptan (fig. 1). With sumatriptan, 77% of attacks were completely resolved within 30 min of treatment, in comparison with 33% following placebo (p = 0.004). Rescue medication with 100% oxygen was required by only 13% of patients 15 min after an injection of sumatriptan, but was used by 49% of those who received placebo (p < 0.001).

The severity of functional disability and the incidence of ipsilateral conjunctival injection (an indication of autonomic dysfunction) were significantly decreased by sumatriptan in comparison with placebo (p < 0.005) 5, 10 and 15 min after treatment. Most patients were able to function normally within 30 min after the sumatriptan injection, whereas it took up to 60 min for those on placebo to return to normal function. Sumatriptan was well tolerated, with adverse events similar to those reported elsewhere [20].

A subsequent study assessed whether the response was improved by increasing the dose of subcutaneous sumatriptan to 12 mg [21]. In this crossover study, 134 patients were randomized to receive two of three possible treatments by subcutaneous injection: 6 mg sumatriptan, 12 mg sumatriptan or placebo. The response to 6 mg sumatriptan for headache relief was similar to that in the earlier study [18], but doubling the dose of the drug did not significantly improve the response rate (fig. 2). In comparison with placebo, sumatriptan significantly (p < 0.001) reduced the need for rescue medication (100% oxygen inhalation), and significantly (p < 0.001) increased the proportion of patients who were able to function normally at 10 or 15 min. However, as with headache relief, there were no significant differences between the two doses of sumatriptan in these measures of efficacy.

Although the adverse events associated with 12 mg sumatriptan were in general similar in nature and severity to those observed after the 6 mg dose, the incidence of adverse events was somewhat higher. Since there was no incremental benefit with the 12 mg dose, subcutaneous sumatriptan 6 mg is recommended for the acute treatment of cluster headache attacks.

A long-term, open, multinational study of the efficacy of sumatriptan (6 mg subcutaneously) in the acute treatment of cluster headache is underway. Preliminary results from the first 3 months of the study [22] indicate that the efficacy of sumatriptan is maintained, with over 70% of patients reporting headache relief at 15 min. There was no evidence that repeated use of sumatriptan increased the frequency of the attacks or reduced the effectiveness of the drug, and the adverse event pattern was unchanged.

A case report has been published [23] of a 32 year-old man who received a total of 480 injections of subcutaneous sumatriptan 6 mg for the treatment of acute attacks of chronic cluster headache over an 11-month period. More than 90% of the attacks resolved within 10 min of treatment (average 6.8 ± 3.4 min). The average duration of 61 attacks over the same period that were treated with analgesics and/or oxygen inhalation instead of sumatriptan was 56.1 ± 20.8 min. There was no evidence of tachyphylaxis and sumatriptan was well tolerated, with no signs of any haematological, biochemical or urinary abnormalities. Electrocardiograms recorded before and during the trial showed no abnormalities.

While sumatriptan is an effective acute treatment for cluster headache it does not prevent attacks within a cluster period when administered pre-emptively. In a placebo-controlled parallel-group study, the effect of 1 week's pre-emptive treatment with oral sumatriptan (100 mg three times a day) on the frequency and severity of cluster headache attacks during an established cluster headache period was investigated. A reduction in headache attack frequency of 50% or more occurred in 23% of patients on sumatriptan and 22% of those on placebo [24].

Conclusions

Cluster headache is a severe and rare form of headache involving trigeminovascular activation. Subcutaneous injection of sumatriptan 6 mg is a rapid and very effective acute treatment for cluster headache. Preliminary results from long-term studies indicate that efficacy is maintained with repeated use, and that the drug is well tolerated.

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