Subcutaneous Octreotide in Cluster Headache: Randomized Placebo-Controlled Double-Blind Crossover Study

Manjit S. Matharu, MBCLB,[1] Miles J. Levy, MBBS[1,2] Karim Meeran, MD,[2] and Peter J. Goadsby, MD, PhD[1]

Current practical evidence-based acute treatments of cluster headache are limited to subcutaneous and intranasal formulations of sumatriptan, and oxygen. Two small randomized, double-blind trials suggested efficacy of somatostatin in cluster headache. We sought to determine whether octreotide, a somatostatin analog, is effective in the abortive treatment of acute cluster headache. Patients with episodic and chronic cluster headache, as defined by the International Headache Society, were recruited to a double-blind placebo-controlled crossover study. Patients were instructed to treat two attacks of at least moderate pain severity, with at least a 24-hour break, using subcutaneous octreotide 100μg or matching placebo. The primary end point was the headache response defined as very severe, severe, or moderate pain becomes mild or nil, at 30 minutes. The primary end point was examined using a multilevel analysis approach. A total of 57 patients were recruited of whom 46 provided efficacy data on attacks treated with octreotide and 45 with placebo. The headache response rate with subcutaneous octreotide was 52%, whereas that with placebo was 36%. Modeling the treatment outcome as a binomial where response was determined by treatment, using the patient as the level 2 variable, and considering period effect, sex, and cluster headache type as other variables of interest, we found that the effect of subcutaneous octreotide 100μg was significantly superior to placebo ($p < 0.01$). Subcutaneous octreotide 100μg is effective in the acute treatment of cluster headache when compared with placebo. Nonvasconstrictor treatment of acute cluster headache is possible.

Ann Neurol 2004;56:488–494

Cluster headache (CH) is the most severe form of primary neurovascular headache. It is characterized by excruciating pain lasting 15 to 180 minutes.[1] Controlled evidence exists to treat acute attacks of CH with oxygen inhalation,[2] intranasal[3] and injectable[4] sumatriptan, high-dose oral zolmitriptan,[5] and intranasal dihydroergotamine.[6] An unequivocally nonvasoconstrictor treatment for acute CH is not available.

Inhalation of oxygen is effective and safe but is impractical for some patients.[7] Injectable and intranasal sumatriptan are highly effective with a rapid onset of action,[4,8] are portable, and have no tachyphylaxis even with frequent use in prolonged cluster bouts.[9] However, the drawbacks of sumatriptan include the need for an injection with the subcutaneous formulation, the limitation of the number of daily doses that can be administered, the incidence of adverse effects especially with the subcutaneous formulation, and the considerable cost of each dose. Oral zolmitriptan has been demonstrated to be of only modest efficacy in acute episodic cluster headache at relatively high dose[10] when compared with its use in migraine,[11] thereby rendering it of limited utility in clinical practice. Intranasal dihydroergotamine has been reported to be better than placebo, but the time to onset of response was not defined and the study used pre-International Headache Society (IHS) diagnostic criteria.[12] In addition, ergots and triptans are contraindicated in patients with vascular disease. Caution must be exercised in patients with CH, because the disorder predominates in middle-aged men, who often have risk factors for cardiovascular disease, particularly smoking.[13–15] Given the limitations of the available agents, some patients do not have an acceptable abortive treatment option. There is therefore a compelling need to develop new pharmacological approaches to CH, particularly, if possible, approaches without vascular effects, to effectively and safely treat these patients. Moreover, the question of whether a nonvasoconstrictor approach might be effective would offer a fundamental insight into the more generic issue of whether cranial vessels provide important nociceptive input in this form of primary headache.

From the [1]Headache Group, Institute of Neurology, Queen Square; and [2]Department of Endocrinology, Hammersmith and Charing Cross Hospitals, London, United Kingdom.

Received Mar 5, 2004, and in revised form Jun 3. Accepted for publication Jun 3, 2004.

Published online Sep 30, 2004, in Wiley InterScience (www.interscience.wiley.com)., DOI: 10.1002/ana.20210

Address correspondence to Dr Goadsby, Institute of Neurology, Queen Square, London, WC1N 3BG UK.
E-mail: peterg@ion.ucl.ac.uk

An acute cluster attack is associated with the release of calcitonin gene related peptide (CGRP) and vasoactive intestinal polypeptide (VIP), whereas triptans, serotonin 5-HT-$_{1B/1D}$ agonists,[16] attenuate the levels of these neuropeptides during successfully treated attacks, thereby implying that the inhibition of these neuropeptides is an important mechanism for aborting a cluster attack.[17,18] It is therefore attractive to study other compounds that may inhibit the release of these neuropeptides but do not have concomitant vascular effects. Somatostatin, an endogenously occurring 14–amino acid peptide, has been shown to inhibit the release of numerous vasoactive peptides, including CGRP[19] and VIP.[20] Two studies have evaluated the abortive effect of somatostatin in migraine. In the first study, intravenous somatostatin (25μg/min for 20 minutes) was compared with treatment with ergotamine (250 μg intramuscularly), or placebo in a double-blind trial comprising 72 attacks in 8 patients.[21] Infusion of somatostatin reduced the maximal pain intensity and the duration of pain significantly compared with placebo, and to a degree comparable to intramuscular ergotamine. In another randomized, double-blind study, subcutaneous somatostatin was compared with ergotamine.[22] Five patients were treated for three attacks by each of the drugs. Subcutaneous somatostatin and ergotamine were equally beneficial regarding effects on maximal pain intensity and the pain area, but somatostatin was less effective in reducing the duration of pain. This limited evidence of the beneficial effect of somatostatin needs to be explored further in properly controlled and adequately powered studies.

The problem with studying native somatostatin as a potential abortive agent for CH is that its short half-life of several minutes necessitates an intravenous infusion, making larger placebo-controlled trials very difficult.[23] Octreotide, a somatostatin analog with a half-life of approximately 1.5 hours,[23] is an attractive compound to study because it can be given subcutaneously, making it possible to recruit larger numbers of patients for a trial on an outpatient basis. In this study, we sought to determine whether octreotide is an effective abortive agent for the acute treatment of CH. We sought a proof-of-principle for both octreotide and a nonvascular approach, so we did not attempt a comparison with existing therapies as such. The data have been presented in preliminary form at the XIth Congress of the International Headache Society, in Rome on September 13–16, 2003.[24]

Patients and Methods

Patients

Patients, men or women between 18 and 65 years of age, with an established diagnosis of CH according to the IHS,[12] and consistent with its revised second edition,[1] were recruited from our center through our contacts with the UK patient organization. Patients were required to have cluster headache attacks of at least 45 minutes' duration when untreated. Exclusion criteria included pregnancy and lactation; frequent migraine or tension-type headaches (>10 days/month); inability to distinguish between migraine and CH; patients who were receiving prophylactic treatment; diabetes mellitus or with known cholelithiasis.

Design

This was a randomized, double-blind, two-attack, crossover study of subcutaneous octreotide 100μg and matching placebo. Octreotide and placebo were packaged into identical prefilled vials each containing 1ml of fluid. Normal saline was used as placebo. All drugs were kept refrigerated in the National Hospital for Neurology and Neurosurgery pharmacy department for the duration of the trial. All patients were taught how to draw up the treatment from the vial with a syringe and to self-administer the subcutaneous injection. They were given the opportunity to practice the injecting in supervised conditions. Participants were instructed to keep the trial drugs refrigerated until used. Patients were asked to treat two attacks, at least 24 hours apart, with either octreotide or matching placebo in a randomized order. They were instructed to grade attacks on an ordinal categorical scale of none, mild, moderate, severe, or very severe.[25] Subsequent assessments were at 5, 10, 15, 20, 30, and 60 minutes. Escape medication was allowed at 30 minutes after dose, usually injectable or intranasal sumatriptan, oxygen, or an analgesic, but not an ergotamine derivative.

Efficacy Assessments

The primary outcome measure was headache response at 30 minutes, a reduction in headache from moderate, severe, or very severe to nil or mild. Secondary outcome measures included the percentage of patients headache-free at 30 minutes, rate of relief of associated symptoms, time to initial relief, and rate of meaningful relief. Associated symptoms, such as vomiting, nausea, photophobia, phonophobia, lacrimation, nasal congestion, and other autonomic features, were recorded immediately before treatment and at 30 minutes. Initial relief was defined as the time that a patient recorded any headache relief. Patients were asked if they considered the response at 30 minutes meaningful. Finally, adverse events were assessed by comparison of tolerability of octreotide to placebo.

Statistical Analysis

Using the results of a crossover study of subcutaneous sumatriptan versus placebo[4], and requiring a treatment difference between placebo and active of 30%, we calculated (Sample Power; SPSS, Chicago, IL) that 42 patients were needed for the study to have an 80% power to detect a difference at an α of 5%. The outcome data were treated as binary: headache response or none at 30 minutes. Considering that attacks 1 and 2 are not strictly independent because the patients remain the same, a multilevel multivariate analysis[26] was performed using software developed by the Multilevel Project, MlwiN (http://multilevel.ioe.ac.uk/).[3] We modeled the effect of active treatment based on attack order, sex, and cluster headache type, using $p < 0.05$ as the level of significance for our testing.

Approval

The study was performed in accordance with the ethical principles of the Declaration of Helsinki. The Joint Ethics Committees of the National Hospital for Neurology and Neurosurgery and Institute of Neurology, London, reviewed and approved the protocol before commencing the study. Medicines Control Agency (UK) approval was obtained for the administration of octreotide as part of a clinical trial. All patients gave informed consent before entering the study. The study protocol was written by us. The pharmaceutical company provided the study medication, but, consistent with recent guidelines,[27] had no influence on or involvement in the conduct of the study, the analysis, or publication of the results.

Results

A total of 57 patients were recruited, 45 men and 12 women, with a mean age of 40 ± 10 years (mean ± standard deviation [SD]).

Disposition of Patients

Of the 57 patients recruited, 6 came to the end of the bout before completing the study; one of these treated the first attack. Two patients withdrew before treating any attacks, and two were lost to follow-up; whether they treated or did not treat attacks was not clear. We have considered them as though they did not treat any attacks. Two attacks of mild severity were treated, and before the treatment of two attacks the syringe malfunctioned; hence, the patients were unable to treat the attacks; these four attacks were excluded from the analysis. Use of escape medication before 30 minutes after treatment was reported in five attacks, which then were scored as outcome failures (Fig 1).

Clinical Features of Study Cohort

The mean duration of cluster headache history was 14 ± 9 years (mean ± SD). Forty-one patients had episodic CH, 15 patients had chronic CH, and 1 episode was unclassifiable because it was the first bout. The average bout length of the patients with episodic cluster headache was 9 ± 5 weeks (mean ± SD). The average attack duration at recruitment was reported by the patients to be 107 ± 75 minutes (mean ± SD; Table 1). Thirty-seven patients had previously used sumatriptan by injection, of whom 36 were responsive; 25 had used intranasal sumatriptan, of whom 16 were responsive; and 38 had used oral sumatriptan, of whom 12 were responsive. In terms of previous use of oxygen, 15 had used high-dose and high-flow oxygen, of whom 9 were responsive; 9 used low-dose or low flow-rate oxygen, of who 4 were responsive.

Overall Efficacy

The primary end point of the study was the combined, attack 1 and 2, headache response rate to octreotide at 30 minutes compared with placebo. The Wald test was significant for the overall regression ($\chi^2 = 14.1$, $p = 0.007$) with only the treatment term being significantly different from zero. There was no significant effect of treatment order, cluster headache type, or sex.

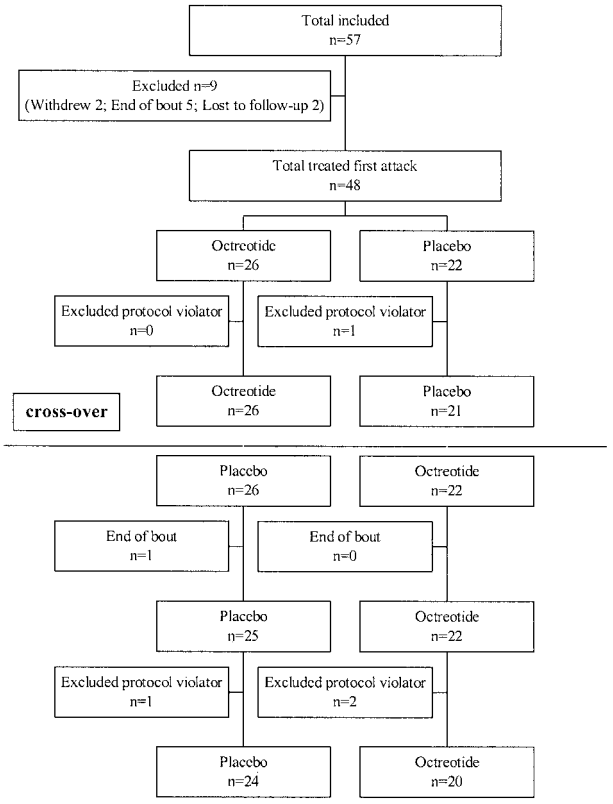

Fig 1. Flowchart showing the disposition of patients in the study.

Efficacy Results

In total, 46 attacks were treated with octreotide and 45 with placebo. In the octreotide-treated attacks, 24 pa-

Table 1. Demographic Data and Cluster Headache Characteristics of 57 Included Patients

Characteristic	Patients (n = 57; %)
Age, years (mean ± SD)	40 ± 10
Sex, n (%)	
Male	45 (79)
Female	12 (21)
Type of CH n (%)	
Episodic	41 (72)
Chronic	15 (26)
Unclassifiable	1 (2)
Average attack duration min	107 ± 75
45–60	21 (37)
61–90	14 (25)
91–180	16 (28)
>180	6 (11)
Average duration of bout, weeks (episodic patients, n = 41)	9 ± 5
CH history, yr	14 ± 9

SD = standard deviation; CH = cluster headache.

tients reported headache relief at 30 minutes (52%) compared with 16 (36%) patients who treated an attack with placebo. Fifteen patients were pain-free at 30 minutes (33%) when treated with octreotide, compared with six (13%) when the attack was treated with placebo ($\chi^2 = 9.8$, $p = 0.04$; Fig 2).

Associated Symptoms

To evaluate the associated symptoms, we included only patients who had the symptom immediately before treatment in the analysis. Conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, ptosis, eyelid edema, and photophobia were the most frequently mentioned. In the attacks treated with octreotide, more patients experienced relief from associated symptoms at 30 minutes (Fig 3).

Time to Initial Relief

The mean time to initial relief in the octreotide-treated group was 18.3 ± 8.9 minutes, compared with 18.1 ± 7.0 minutes in the placebo-treated group.

Meaningful Relief

Patients were asked if they thought the cluster headache attack was adequately treated at 30 minutes. Seventeen (37%) patients who treated an attack with octreotide reported meaningful relief, compared with 13 (29%) patients who had treated an attack with placebo.

Escape Medication

The frequency of use of escape medication was lower in octreotide-treated attacks compared with those treated with placebo, 20 (44%) vs 25 (56%).

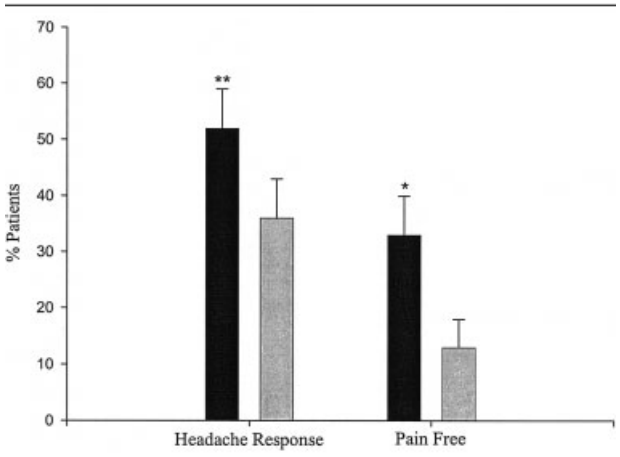

Fig 2. Efficacy: headache response (a reduction of headache intensity from very severe, severe, or moderate to mild or no pain) and pain-free rates (no pain) at 30 minutes after treatment with octreotide (black bars) *versus placebo* (gray bars). $^{**}p < 0.01$; $^{*}p < 0.05$.

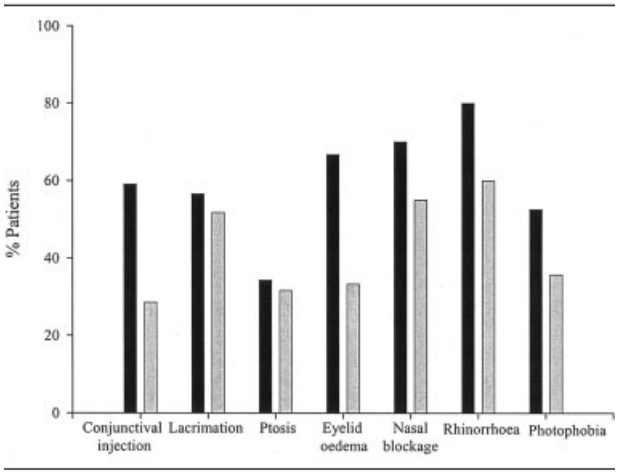

Fig 3. Percentage of patients reporting improvement of associated symptoms with octreotide (black bars) *and placebo* (gray bars) *at 30 minutes. Only patients with symptoms at baseline were included. Because of multiple-comparison issues, no statistical analysis was performed.*

Tolerability

No serious adverse effects were reported with either the octreotide or placebo-treated attacks. Eight patients treated with octreotide (17%) reported minor gastrointestinal disturbance, including nausea, abdominal bloating, and diarrhea, compared with four patients (9%) treated with placebo. The adverse events are shown in Table 2. All resolved spontaneously and were generally short-lived and mild in nature.

Discussion

To our knowledge, this is the first placebo-controlled trial investigating the potential use of octreotide in the treatment of acute cluster headache attacks. It demonstrates that octreotide is effective and well tolerated in cluster headache attacks that normally last longer than 45 minutes. Headache response within 30 minutes was reported in 52% of the attacks that were treated with octreotide, compared with 36% of the attacks treated with placebo. Octreotide was also superior to placebo regarding pain-free rates, treatment of associated symptoms, and meaningful relief. This study establishes a

Table 2. Adverse Events among Patients with Cluster Headache Attacks Treated with Octreotide or Placebo

Adverse Event	Octreotide	Placebo
Diarrhea, abdominal Bloating or nausea	8	4
Dull background headache	3	1
Lethargy	2	1
Injection-site reaction	2	1
Dizziness	1	0
Loss of libido	1	0
Facial flushing	1	0

clear principle: that vasoconstrictor action is not necessary to abort acute cluster headache.

We have not compared octreotide with sumatriptan in this study, but given the results of studies of sumatriptan 6mg by injection[4,8] and 20mg by nasal spray,[3] octreotide seems inferior to both of these formulations of sumatriptan for the population response rate and time to initial relief. However, octreotide is not contraindicated in ischemic heart disease, suggesting that it may have a role as an alternative therapeutic strategy to oxygen in patients who cannot take 5-$HT_{1B/1D}$ receptor agonists. It is important to recall that the effect in responders is no less than the effect of injectable sumatriptan, because the response end point is identical, but that the study suggests the population of responders is smaller.

Octreotide was well tolerated with no reports of serious side effects. The main side effect observed was gastrointestinal upset in eight patients treated with octreotide compared with four patients treated with placebo. All side effects resolved spontaneously and were generally short-lived and mild in nature. The side effects reported in this study were in keeping with the reported experience of side effects with this drug.[28] The good tolerability data make octreotide an attractive agent in a condition in which repeated doses will be required over a relatively short period. However, our study does not directly address the issue of long-term tolerability of subcutaneous octreotide in CH, because only a single active dose was administered. This issue of long-term tolerability of octreotide has been addressed in several studies in acromegaly that require octreotide three times daily for life. Case reports of symptomatic gallstones initially caused concern, and the prevalence of gallstones rises in patients who are screened. However, the risk of symptomatic gallstones is extremely low, and, in one study of regular administration of octreotide LAR for a year, there were no cases of gallstones.[29] Hence, the prolonged use of octreotide in CH, with its concomitant devastating morbidity from the excruciating pain, will need to be balanced against the risk of developing gallstones.

We used the crossover approach because attacks are relatively stereotyped, and the attacks occur in rapid succession. Hence, fewer patients are required in a relatively rare disorder. However, treatment of two separate attacks in the same patient means that the attacks are not strictly independent. We therefore used a multilevel multivariate statistical approach.[26,30] Our analysis showed no influence of the order in which the treatment was given. Moreover, the use of the multilevel multivariate approach permits consideration of all the relevant data in a single analysis. We have used this analysis in a randomized controlled trial of sumatriptan nasal spray in cluster headache,[3] and it is attractive in this setting.

There are some limitations of this study that require consideration. First, we were obliged to notify patients about potential gastrointestinal side effects from octreotide when consenting patients for the study, in line with the requirements of the local ethics committee. This may have introduced an element of unblinding to the study in the patients who experienced these symptoms, which may have biased the results. This did not manifest as a significant ordering effect in the analysis. Second, this was a single-dose study, and long-term studies would need to be performed to determine the long-term use of this medication, because cluster headache is a chronic condition. Third, the study population consisted of 72% episodic cluster patients and 26% chronic patients. Although we did not see a difference in response between the two, we did not power the study to dissect the more common episodic from chronic cluster headache. A separate study of chronic cluster headache may show less robust results, which would, on the other hand, predict a better outcome in episodic cluster headache should a larger study in that subgroup be done. Last, this is a single-center study. Our unit acts as a referral center for the entire UK National Health Service; therefore, our patient mix is taken from across the United Kingdom. This is not a substitute for a multicenter study but for a proof-of-principle study done independent of industry support seems reasonable way forward.

What are the potential modes of action of somatostatin and its analogs in cluster headache? Somatostatin is a neuromodulator and neurotransmitter that is extensively distributed within the nervous system. Neurons containing somatostatin are found in the regions of the central and peripheral nervous system involved in nociception, such as peripheral sensory fibers, dorsal horn of the spinal cord, trigeminal nucleus caudalis, periaqueductal gray, and the hypothalamus.[31,32] Somatostatin mediates its actions by binding to high-affinity membrane receptors. Five somatostatin receptors (sst_{1-5}) have been cloned,[33] with octreotide acting predominantly on sst_2 and sst_5.[34] Octreotide is a nonlipophilic compound and is believed to poorly penetrate the blood–brain barrier, thereby suggesting that its target of action is the peripheral nervous system. This peripheral mode of action may involve inhibition of release of vasoactive substances, such as CGRP[19] and VIP,[20] which have been implicated in the pathophysiology of CH.[35] It may be the case that the peripheral action limits the effectiveness of octreotide, and we would strongly wish to test a brain penetrant compound in the future.

Notwithstanding that octreotide is believed to poorly penetrate the blood–brain barrier, it may be able to access the central nervous system to some extent during the headache attacks. It has been proposed that the blood—brain barrier may become leaky during the headache phase.[36,37] Sumatriptan, which has un-

doubted efficacy in CH and poorly penetrates the blood–brain barrier,[38] has been shown to be effective even in the presence of trigeminal nerve root section,[39] thereby strongly suggesting a central site of action which may be accessed via a leaky blood–brain barrier. The potential central sites of action of octreotide include the hypothalamus, periaqueductal gray, and trigeminal nucleus caudalis. Functional imaging with positron emission tomography,[40] structural imaging with voxel-based morphometry,[41] and exciting results with deep brain stimulation[42] have identified the posterior hypothalamic gray matter as the key area for the basic defect in CH. Given that the hypothalamus is the chief source of somatostatin within the central nervous system,[43] the alteration in hypothalamic activity in CH may result in the disinhibition of descending somatostatinergic pathways to the trigeminal nucleus caudalis, either directly or via the periaqueductal gray. There is evidence that the periaqueductal gray and trigeminal nucleus caudalis are under tonic inhibition from the hypothalamus.[44] The disinhibition of descending input caused by hypothalamic dysfunction theoretically could result in uncontrolled trigeminovascular activation, as seen during a cluster headache attack. This hypothetical state of reduced somatostatinergic inhibitory activity may explain the observation of reduced somatostatin levels during CH,[45] as well as the therapeutic effect of administering exogenous somatostatin[21,22] and octreotide, as found in this study.

Our results are interesting in the context of primary headache more generally. It has been reported in a small study with a nonstandard end point that octreotide is useful in migraine.[46] However, we have recently conducted a double-blinded placebo-controlled trial powered to detect a 30% difference with placebo and found no effect.[47] In this context, it is noteworthy that somatostatin by infusion does not trigger headache in migraine sufferers, cluster headache patients, or controls.[48] Moreover, the striking difference between migraine and cluster headache in the pattern of brain activation on functional imaging, where cluster headache patients activate the posterior hypothalamus,[40,49,50] and both episodic[51,52] and chronic[53] migraine the brainstem without hypothalamic activation, is in keeping with greater prominence of a somatostatinergic mechanisms in cluster headache. If this were so, this study would be the first substantial evidence for a pharmacologically based difference in the acute treatment of these disorders, which are so strikingly clinically different.

In animal studies, somatostatin has been found to differentially modify the release of a variety of neurotransmitters in several regions of the brain. Serotonin release from rat hypothalamic, cortical, and hippocampal slices is enhanced by somatostatin,[54] as is noradrenaline release from the cortex,[55] whereas noradrenaline release is inhibited in the rat hypothalamus[56] and chick sympathetic ganglia.[57] Somatostatin inhibits the release of γ-amino butyric acid in the rat striatum,[58] whereas dopamine release is enhanced.[59] Further studies will be required to understand the mechanism of action of somatostatin and its analogs in CH.

In conclusion, to our knowledge, this is the first adequately powered placebo-controlled study to demonstrate the effectiveness of a somatostatin analog in the treatment of acute cluster headache attacks. In clinical practice, octreotide may have a particular utility in patients who are unresponsive to or intolerant of $5HT_{1B/1D}$ agonists and oxygen, and as an alternative to oxygen in patients with cardiovascular disease. Furthermore, this study demonstrates that somatostatin analogs, which have no vasoconstrictor effect, offer a novel therapeutic approach to the treatment of acute cluster headaches that may offer insights into understanding more fundamental aspects of this disabling form of primary headache.

This study was supported by the Institute of Neurology, London and the Wellcome Trust (P.J.G.).

References

1. Headache Classification Committee of The International Headache Society. The International Classification of Headache Disorders. 2nd ed. Cephalalgia 2004;24:1–160.
2. Fogan L. Treatment of cluster headache: a double blind comparison of oxygen vs air inhalation. Arch Neurol 1985;42:362–363.
3. van Vliet JA, Bahra A, Martin V, et al. Intranasal sumatriptan in cluster headache- randomized placebo-controlled double-blind study. Neurology 2003;60:630–633.
4. Ekbom K, The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. N Engl J Med 1991;325:322–326.
5. Bahra A, Gawel MJ, Hardebo J-E, et al. Oral zolmitriptan is effective in the acute treatment of cluster headache. Neurology 2000;54:1832–1839.
6. Andersson PG, Jespersen LT. Dihydroergotamine nasal spray in the treatment of attacks of cluster headache. Cephalalgia 1986; 6:51–54.
7. Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalalgias and hemicrania continua. Drugs 2003; 63:1637–1677.
8. Ekbom K, Monstad I, Prusinski A, et al. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. Acta Neurol Scand 1993;88:63–69.
9. Ekbom K, Waldenlind E, Cole JA, et al. Sumatriptan in chronic cluster headache: results of continuous treatment for eleven months. Cephalalgia 1992;12:254–256.
10. Bahra A, Gawel M, Hardebo J-E, et al. Oral zolmitriptan is effective in the acute treatment of cluster headache. Neurology 2000;55:1239.
11. Palmer KJ, Spencer CM. Zolmitriptan. CNS Drugs 1997;7: 468–478.
12. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8:1–96.
13. Kudrow L. Cluster headache. In: Blau JN, ed. Headache: Clinical, Therapeutic, Conceptual and Research Aspects. London: Chapman and Hall, 1987.

14. Sjaastad O. Cluster headache syndrome. London: Saunders, 1992.
15. Manzoni GC, Terzano MG, Bono G, et al. Cluster headache—clinical findings in 180 patients. Cephalalgia 1983;3:21–30.
16. Goadsby PJ. The pharmacology of headache. Prog Neurobiol 2000;62:509–525.
17. Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache. Brain 1994;117: 427–434.
18. Fanciullacci M, Alessandri M, Figini M, et al. Increase in plasma calcitonin gene-related peptide from extracerebral circulation during nitroglycerin-induced cluster headache attack. Pain 1995;60:119–123.
19. Helyes Z, Pinter E, Nemeth J, et al. Anti-inflammatory effect of synthetic somatostatin analogues in the rat. Br J Pharmacol 2001;134:1571–1579.
20. Fassler JE, O'Dorisio TM, Mekhjian HS, Gaginella TS. Octreotide inhibits increases in short-circuit current induced in rat colon by VIP, substance P, serotonin and aminophylline. Regul Pept 1990;29:189–197.
21. Sicuteri F, Geppetti P, Marabini S, Lembeck F. Pain relief by somatostatin in attacks of cluster headache. Pain 1984;18: 359–365.
22. Geppetti P, Brocchi A, Caleri D, et al. Somatostatin for cluster headache attack. In: Pfaffenrath V, Lundberg PO, Sjaastad O, eds. Updating in headache. Berlin, Heidelberg, New York, Tokyo: Spring-Verlag, 1985:302–305.
23. Harris AG. Somatostatin and somatostatin analogues: pharmacokinetics and pharmacodynamic effects. Gut 1994;35:S1–S4.
24. Matharu MS, Levy MJ, Meeran K, Goadsby PJ. Subcutaneous octreotide is effective in the treatment of acute cluster headache: a double-blind placebo-controlled crossover study. Cephalalgia 2003;23:580.
25. Pilgrim AJ. Methodology of clinical trials of sumatriptan in migraine and cluster headache. Eur Neurol 1991;31:295–299.
26. Snijders TAB, Bosker RJ. Multilevel analysis. An introduction to basic and advanced multilevel modelling. 1st ed. London: Sage Publications, 1999:266.
27. Rosenberg RN, Aminoff M, Boller F, et al. Reporting clinical trials: full access to all the data. Eur J Neurol 2002;9:123–124.
28. Newman CB, Melmed S, Snyder PJ, et al. Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients—a clinical research center study. J Clin Endocrinol Metab 1995;80:2768–2775.
29. Lancranjan I, Atkinson AB. Results of a European multicentre study with Sandostatin LAR in acromegalic patients. Sandostatin LAR Group. Pituitary 1999;1:105–114.
30. Yang M, Goldstein H, Heath A. Multilevel models for repeated binary outcomes: attitudes and voting over the electoral cycle. J R Stat Soc (A) 2000;163:49–62.
31. Krisch B. Hypothalamic and extrahypothalamic distribution of somatostatin-immunoreactive elements in the rat brain. Cell Tissue Res 1978;195:499–513.
32. Schindler M, Holloway S, Hathway G, et al. Identification of somatostatin sst2(a) receptor expressing neurones in central regions involved in nociception. Brain Res 1998;798:25–35.
33. Hoyer D, Bell GI, Berelowitz M, et al. Classification and nomenclature of somatostatin receptors. Trends Pharmacol Sci 1995;16:86–88.
34. Patel YC, Srikant CB. Subtype selectivity of peptide analogs for all five cloned human somatostatin receptors (hsstr 1-5). Endocrinology 1994;135:2814–2817.
35. Edvinsson L, Goadsby PJ. Neuropeptides in migraine and cluster headache. Cephalalgia 1994;14:320–327.
36. Harper AM, MacKenzie ET, McCulloch J, Pickard JD. Migraine and the blood-brain barrier. Lancet 1977;1:1034–1036.
37. Goadsby PJ. Current concepts of the pathophysiology of migraine. In: Mathew NT, ed. Neurologic clinics of North America. Vol 15. Philadelphia: Saunders, 1997:27–41.
38. Kaube H, Hoskin KL, Goadsby PJ. Inhibition by sumatriptan of central trigeminal neurones only after blood-brain barrier disruption. Br J Pharmacol 1993;109:788–792.
39. Matharu MS, Goadsby PJ. Persistence of attacks of cluster headache after trigeminal nerve root section. Brain 2002;175:976–984.
40. May A, Bahra A, Buchel C, et al. Hypothalamic activation in cluster headache attacks. Lancet 1998;352:275–278.
41. May A, Ashburner J, Buchel C, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 1999;5:836–838.
42. Leone M, Franzini A, Bussone G. Stereotatic stimulation of the posterior hypothalamic gray matter in a patient with intractable cluster headache. N Engl J Med 2001;345:1428–1429.
43. Swaab DF, Hofman MA, Lucassen PJ, et al. Functional neuroanatomy and neuropathology of the hypothalamus. Anat Embryol 1993;187:317–330.
44. Lumb BM. Inescapable and escapable pain is represented in distinct hypothalamic-midbrain circuits: specific roles for Adelta- and C-nociceptors. Exp Physiol 2002;87:281–286.
45. Caleri D, Marabini S, Panconesi A, Pietrini U. A pharmacological approach to the analgesizing mechanism of somatostatin in cluster headache. Ric Clin Lab 1987;17:155–162.
46. Kapicioglu S, Gokce E, Kapicioglu Z, Ovali E. Treatment of migraine attacks with a long-acting somatostatin analogue (octreotide, SMS 201-995). Cephalalgia 1997;17:27–30.
47. Levy MJ, Matharu MS, Bhola R, et al. Octreotide is not effective in the acute treatment of migraine. Cephalalgia (in press).
48. Levy M, Matharu MS, Bhola R, et al. Somatostatin infusion withdrawal: a study of patients with migraine, cluster headache and healthy volunteers. Pain 2003;102:237–242.
49. May A, Bahra A, Buchel C, et al. PET and MRA findings in cluster headache and MRA in experimental pain. Neurology 2000;55:1328–1335.
50. Sprenger T, Boecker H, Tolle TR, et al. Specific hypothalamic activation during a spontaneous cluster headache attack. Neurology 2004;62:516–517.
51. Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. Nat Med 1995;1:658–660.
52. Bahra A, Matharu MS, Buchel C, et al. Brainstem activation specific to migraine headache. Lancet 2001;357:1016–1017.
53. Matharu MS, Bartsch T, Ward N, et al. Central neuromodulation with implanted suboccipital stimulators in patients with chronic migraine. Cephalalgia 2003;23:655.
54. Tanaka S, Tsujimoto A. Somatostatin facilitates the serotonin release from rat cerebral cortex hippocampus and hypothalamus slices. Brain Res 1981;208:219–222.
55. Tsujimoto A, Tanaka S. Stimulatory effect of somatostatin on norepinephrine release from rat brain cortex slices. Life Sci 1981;28:903–910.
56. Gothert M. Serotonin-receptor-mediated modulation of Ca^{2+}-dependent 5-hydroxytryptamine release from neurones of the rat brain cortex. Naunyn Schmiedebergs Arch Pharmacol 1980; 314:223–230.
57. Boehm S, Huck S. A somatostatin receptor inhibits noradrenaline release from chick sympathetic neurons through pertussis toxin-sensitive mechanisms: comparison with the action of alpha 2-adrenoceptors. Neuroscience 1996;73:595–604.
58. Meyer DK, Conzelmann U, Schultheiss K. Effects of somatostatin-14 on the in vitro release of [3H]GABA from slices of rat caudatoputamen. Neuroscience 1989;28:61–68.
59. Chesselet MF, Cheramy A, Romo R, et al. GABA in the thalamic motor nuclei modulates dopamine release from the two dopaminergic nigrostriatal pathways in the cat. Exp Brain Res 1983;51:275–282.