Short report

Indomethacin-responsive episodic cluster headache

DP GEANEY

From the MRC Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford, UK

SUMMARY The case of a man with a 34 year history of episodic cluster headaches is described. At the peak of a cluster the headaches occurred up to twenty times a day. The headaches were unresponsive to conventional therapy but were dramatically abolished by indomethacin. This effect of indomethacin was confirmed in a double-blind placebo-controlled trial.

Case report

A man aged 52 years had suffered from episodic headaches for 34 years. These consisted of intense rapidly pulsating pain in the left retro-orbital region radiating to the left maxilla, left upper teeth and gum margin, and the left temple. They were associated with reddening and watering of his left eye, drooping of his left eyelid, and a blocked sensation in his left nostril. The headaches occurred in clusters lasting for 3-8 weeks followed by a completely symptomless period of 6-20 weeks. Each headache lasted from 10-30 minutes, and these built up in frequency and intensity during the cluster, occurring up to 20 times in 24 hours and being most severe during the night.

Examination at the age of 36 years revealed an abnormal left pupil, variably recorded as smaller or larger than the right and constricting on accommodation but unresponsive to direct or consensual light. All investigations, including syphilis serology, were normal except for a left carotid angiogram which revealed a small anterior communicating artery aneurysm which was not felt to be relevant to his complaint.

His headaches failed to respond to ergotamine, methysergide, chlorpromazine, carbamazepine, clonidine, pizotifen, imipramine, corticosteroids, lithium, many different analgesics and removal of several of the teeth in his left upper jaw. Psychiatric assessments concluded that there was no psychiatric disorder exacerbating or perpetuating the headaches. Acupuncture, avulsion of the left infraorbital nerve and left cervical sympathetic block did not help. At the age of 44 years he had a left trigeminal sensory root section performed via the posterior fossa (the left eighth nerve was particularly viewed and noted to be normal in order to exclude any structural abnormality as he had also gradually developed bilateral sensorineural deafness). For six months following this he was pain-free

but then the headaches recurred in identical fashion but now on the right side. The headaches again failed to respond to conventional therapy and at the age of 50 years it was noted that both pupils were now unresponsive to light but constricted on accommodation with tonic redilation. Weak (0.125%) pilocarpine drops to the eyes induced bilateral miosis, suggesting parasympathetic denervation hypersensitivity (Holmes-Adie syndrome¹).

At the age of 52 years whilst in the middle of a cluster of headaches he was commenced on indomethacin 50 mg four times daily. The response was dramatic since his headaches were immediately abolished after the first dose. He was able to completely eliminate headaches during different stages of a cluster with doses of indomethacin between 25 mg thrice daily and 50 mg four times daily. Between clusters he was asymptomatic on no therapy.

During a subsequent cluster a double-blind placebo-controlled trial was performed and he was asked to record all headaches (fig 1). Two weeks after the onset of a cluster

Fig 1 Headache frequency during indomethacin and placebo treatment.

Address for reprint requests: Dr DP Geaney, MRC Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE, UK.

Received 23 February 1983. Accepted 14 April 1983

he stopped the indomethacin and had three typical headaches during the subsequent twelve hours. The trial was then commenced. During twenty-four hours he took four capsules each containing either 50 mg indomethacin or placebo. On the first day he received four placebo capsules and had eleven headaches (duration 12–18 minutes) during the twenty-four hour period. The subsequent two days he received indomethacin and was completely free of headaches. On the fourth day he again received placebo and had eleven headaches (duration 10–22 minutes). The following three days were again headache-free on indomethacin.

Discussion

This case bears a striking resemblance to a variety of cluster headache called chronic paroxysmal hemicrania which was first described in 1974 by Sjaastad and Dale.^{2,3} This condition was reviewed in 1980⁴ at which time eight definite and ten possible cases were known. Like chronic cluster headache the headaches occurred daily without remission. However, it differed from typical chronic and episodic cluster headache in that the headaches were of shorter duration (usually 10–20 minutes), more frequent (maximum frequency of at least 15 in 24 hours), responded completely to indomethacin, and occurred predominantly in females. Although an initial episodic phase frequently preceded the chronic condition, the present case differs in that the attacks remained exclusively episodic for 34 years.

The mechanism of action of indomethacin in preventing these headaches is uncertain. It may be related to inhibition of prostaglandin synthesis,⁵ but other prostaglandin antagonists have not been associated with this dramatic effect (although aspirin has been noted to be mildly beneficial³). Indomethacin is not generally beneficial in ordinary cluster headache but may be effective in benign exertional headache,⁶ or cluster headache variant⁷ in which frequent daily cluster headaches may be associated with multiple short-lived stabbing pains in the head and a background vascular headache.

The development of bilateral Holmes-Adie pupils in this case is also interesting, particularly as the left pupillary abnormality was noted when the cluster headaches were left-sided, and the right-sided pupillary abnormality developed after the cluster headaches had changed to the right side following section of the sensory root of the left trigeminal nerve. The permanent ocular lesion that has previously been described in cluster headache, however, is Horner's syndrome.⁸ The site of putative structural damage is, of course, poorly localised by this syndrome. In the present case it seems more clearly placed in the ciliary ganglion as severe loss of parasympathetic ganglion cells at this site are found in

the Holmes-Adie syndrome.⁹ Whether such lesions should be regarded as the consequence or the cause of cluster headache is unknown. However, the present case suggests that if causal, the site of the lesion could be peripheral rather than within the hypothalamus as has been previously suggested.^{10,11} If there is an abnormal peripheral autonomic site (in this case the ciliary ganglion), local discharges within it might induce aberrant stimulation of adjacent pain fibres.

Whatever the link between Holmes-Adie pupils and episodic cluster headache in this case, the importance of detecting cases of cluster headache in the indomethacin-responsive group is obvious. It now appears that the group may be expanded to include episodic cluster headaches. However, the distinguishing characteristics of very frequent and short-lived headaches are still present throughout the group.

I thank Dr KMS Peet for permission to report this case, Dr JK Aronson for assistance with the double-blind trial, and Merck, Sharpe & Dohme Ltd for supplying the indomethacin and indomethacin placebo.

References

- 1 Russel GFM. The pupillary changes in the Holmes-Adie syndrome. *J Neurol Neurosurg Psychiatry* 1956;**19**:289–96.
- 2 Sjaastad O, Dale I. Evidence for a new (?) treatable headache entity. *Headache* 1974;**14**:105–8.
- 3 Sjaastad O, Dale I. A new (?) clinical headache entity "chronic paroxysmal hemicrania". *Acta Neurol Scand* 1976;**54**:140–59.
- 4 Sjaastad O, Apfelbaum R, Caskey W, Christoffersen B, Diamond S, Graham J, Green M, Hørven I, Lund-Roland L, Medina J, Rogado S, Stein H. Chronic paroxysmal hemicrania (CPH). The clinical manifestations. A review. *Ups J Med Sci* 1980;**3**, Suppl:27–33.
- 5 Simon LS, Mills JA. Non-steroidal anti-inflammatory drugs. *N Engl J Med* 1979;**302**:1179–85.
- 6 Diamond S, Medina JL. Prolonged benign exertional headache: clinical characteristics and response to indomethacin. *Adv Neurol* 1982;**33**:145–9.
- 7 Medina JL, Diamond S. Cluster headache variant. Spectrum of a new headache syndrome. *Arch Neurol* 1981;**38**:705–9.
- 8 Ekbom K. A clinical comparison of cluster headache and migraine. *Acta Neurol Scand (Suppl)* 1970;**4146**:1–48.
- 9 Harriman DGF. Pathological aspects of Adie's syndrome. *Adv Ophthalmol* 1970;**23**:55–73.
- 10 Kunkle EC. Acetylcholine in the mechanism of headaches of the migraine type. *Arch Neurol Psychiat* 1959;**84**:135.
- 11 Stowell A. Physiologic mechanisms and treatment of histaminic or petrosal neuralgia. *Headache* 1970;**9**:187–94.