

## CHRONIC PAIN SYNDROMES AND THEIR TREATMENT I. CLUSTER HEADACHE

GORDON M. WYANT AND EDWARD M. ASHENHURST

CLUSTER HEADACHE has been known by many names over the years: migrainous neuralgia, histamine cephalgia, sphenopalatine neuralgia and Sluder's syndrome are all synonyms. The condition is characterized by pain localized to one side of the head and face with photophobia, lacrimation, injection of the conjunctiva, nasal congestion and rhinorrhoea, all restricted to the same side as the pain. The pain which is described as excruciatingly severe, boring and, above all, incapacitating, may occur several times during a 24-hour period and is more common in males than in females. An intermittent or episodic type is recognized in which after several weeks or months of daily attacks the patient goes through a period of remission, again lasting from weeks to months; or it may be continuous or chronic in the sense that attacks of pain occur daily or almost daily without remission. These attacks not infrequently occur at night and awaken the patient from his sleep or, if they strike during the day, their great severity will interfere with occupation and enjoyment of life. They are not relieved by lying down. Each attack may last from minutes to several hours and then subsides spontaneously. No specific precipitating environmental factors are recognized, although the intake of alcohol, and at times the administration of histamine, tend to trigger attacks, and in some patients ingestion of food has the same effect. Glyceryl trinitrate will precipitate an attack during the vulnerable phase of the disease.

Cluster headache differs from other types of headache in a number of ways, although at times it may be difficult to distinguish it from atypical forms of migraine or tension headache. However, in most instances the strictly unilateral distribution of the pain with ipsilateral ocular and nasal

manifestations will give a clue to the correct diagnosis. Also true cluster headaches are not preceded by prodromal signs. Although the symptomatology might suggest an aetiology of histamine or serotonin release, antihistaminics and desensitization have proven disappointing, and so has treatment with cimetidine, a histamine H<sub>2</sub> antagonist.<sup>1</sup> Antidepressants, diphenylhydantoin, corticosteroids, and acupuncture have all been tried without success.<sup>2</sup> One case is on record in which the administration of oxygen 10 litres by mask, inhaled through a re-breathing bag, tended to abort headaches in less than 10 minutes.<sup>2</sup> Carbamazepine has been reported as being occasionally successful, as have diazepam, methysergide, indomethacin, and propranolol.<sup>2-4</sup> Parenteral dihydroergotamine and steroid-ergotamine combinations also have been effective.<sup>3,4</sup> With the exception of the surgical extirpation of the sphenopalatine ganglion<sup>5</sup> or section of the greater superficial petrosal nerve,<sup>6,7</sup> none of the other modalities of treatment have been more than occasionally successful and therefore cannot be relied upon to give predictable relief from the very disabling condition. The probability that any particular patient will respond to sphenopalatine ganglionectomy can be determined by precipitating an attack by the ingestion of alcohol, followed by a block of the ganglion with local anaesthetic. A positive test indicates that the operation might be successful in providing relief.

### CLINICAL REPORTS

Ekbom<sup>8</sup> was the first investigator to be struck by the similarity in the cyclic manifestations of manic depressive states and of cluster headache. These observations led him to a trial of lithium in patients suffering from periodic cluster headache, as this had been effective in cyclic psychoses. He found that this treatment gave promising results and his observations were confirmed by Kudrow some years later.<sup>9</sup> On the basis of these reports Mathew<sup>10</sup> assembled a series of 31 patients and was able to report that lithium was an effective prophylactic in both

Gordon M. Wyant, M.D., F.R.C.P.(C), F.F.A.R.C.S., Director, Pain Management Service, University Hospital, Saskatoon, and Plains Health Centre, Regina.

Edward M. Ashenhurst, M.B., B.Ch., B.A.O., F.R.C.P.(Ed), F.R.C.P.(C), Department of Clinical Neurological Sciences, Division of Neurology, University Hospital, Saskatoon, and University of Saskatchewan.

episodic and chronic cluster headache. His success rate was indeed impressive with 55 per cent of patients having more than 90 per cent improvement and only 20 per cent showing no improvement at all.

This report came to our attention when we were faced with the first cluster headache patient in the Pain Management Service at the Plains Health Centre in Regina. Encouraged by our results with this patient we contacted all who had presented with cluster headache at one time or another at University Hospital in Saskatoon. Twenty-two such cases were identified from the records and patients were invited to contact the Pain Management Service. Four responded, but since two were in remission at the time, no treatment could be started. Two other patients were referred to the Service independently, so that this report draws on our experience with a total of five patients, of whom four were afflicted with the continuous and one with the intermittent variety of cluster headache.

The following are brief abstracts of these five cases:

*Patient 1. K.McC.*

This 47-year-old man was first seen in May 1977, at which time he had suffered cluster headaches for the preceding four years on an almost daily basis. He was completely incapacitated whenever the pain occurred, to the extent that it interfered with his activities as a salesman and curtailed his social activities. Attacks were triggered by intake of alcohol, food and physical exercise. He had been seen by a neurologist and had been on a number of medications, none of which had helped him. Antihistaminics and cyproheptadine were tried, all without success, as were general analgesics. He was then started on lithium and on his first return visit stated that "this is the best three weeks I have had yet". He has been on this therapy now for close to one year with amitriptyline having been added more recently. He still gets almost daily headaches but of greatly attenuated intensity and they no longer interfere with his professional and leisure activities.

*Patient 2. A.S.*

This 60-year-old male had left-sided cluster headache for the preceding ten years, which had been somewhat less severe since he was placed on propranolol medication some time before, for angina pectoris. At times he had been able to abort attacks by taking "Cafergot" and estab-

lished attacks were eased by cold compresses. He had seen many specialists over the years in many cities in The United States and Canada and had been submitted to different types of treatment, including cryotherapy, acupuncture and hypnosis, and had received pizotyline.

He was placed on lithium carbonate and more recently amitriptyline was added. This treatment greatly reduced both the severity and frequency of the headaches so that in a period of two weeks he had a mere six headaches, only one of which was of moderate severity and short duration.

*Patient 3. J.H.*

This 44-year-old man had right-sided cluster headache for the last 13 years. He used to have attacks four or five times each day. If the attacks occurred at night they would wake him from his sleep. Acetylsalicylic acid, codeine compound, diphenylhydantoin, "Cafergot", chlordiazepoxide, methysergide and diphenhydramine each only gave moderate relief. Nine years ago he had a section of the superficial petrosal nerve without effect and cryosurgery had given only slight relief. In due course the pain became almost continuous. Acupuncture together with pizotyline gave him some relief but after 18 months the pain recurred with increasing severity and frequency. He was placed on lithium carbonate, of which he required the rather large doses of 600 mg three times daily (t.i.d.). This caused some tremor, but with the later addition of amitriptyline this was reduced gradually to 300 mg t.i.d. He has had no headaches for the past two months.

*Patient 4. H.P.*

This 55-year-old man had periodic left-sided cluster headaches with approximately two vulnerable periods each year. During the vulnerable phase attacks were triggered by the intake of alcohol. He had an intensive course of methysergide as well as many other types of treatment, all without success. He was placed on a course of lithium carbonate and later amitriptyline was added, and this in due course led to complete control of his headaches at a serum level of 1.14 mmol·L. He has remained well since, but it is quite possible that he is now in remission.

*Patient 5. D.K.*

This 34-year-old housewife had cluster headaches for the past four years. Her pain was continuous although she had short periods of remission of about two weeks at a time. Pizotyline eased the intensity of the attacks somewhat, but

did not control them. Eventually she was controlled with a serum lithium level of  $1.28 \text{ mmol} \cdot \text{L}$ . She was bothered by some nausea which was considerably eased by dimenhydrinate. The dose of lithium was reduced and amitriptyline added and she has been comfortable since.

#### DISCUSSION

Since the pathogenesis of cluster headache is unknown and the pharmacological action of lithium is not clear, treatment with this drug must of necessity be empirical. One can only speculate on the mechanism of action of lithium carbonate in cluster headache. Lithium is a monovalent cation and the lightest of the alkali metals which can take the place of sodium in the extracellular fluid and, like sodium, enters the cell during depolarization. Unlike sodium, however, it is not easily removed by the sodium pump and, consequently, potassium is prevented from re-entering the cell. As a result electrolyte balance across membranes is disturbed and membrane potential falls. This then interferes with nerve conduction and with excitability of the neurone. Such a mechanism could have obvious implications in the treatment of cluster headache. It is also known that lithium changes norepinephrine metabolism<sup>11</sup> and, if similar changes in metabolism should also affect serotonin, also a monoamine, one could speculate that this is yet another mechanism of action. This of course presupposes that cluster headache is somehow related to serotonin release, which is by no means certain. Indeed we did attempt to treat one patient with cyproheptadine (Periactin), an antiserotonin drug, without affecting the headache.

To use lithium carbonate safely one must understand its pharmacokinetics. Lithium is readily absorbed from the gastrointestinal tract and plasma levels peak at two to four hours. It is excreted primarily in the urine, being filtered by the glomeruli and re-absorbed in the tubules. In the presence of a healthy kidney, renal clearance is proportional to plasma concentration and approximately half of a single dose is excreted in 24 hours. Therefore it is important that renal function be adequate, since otherwise serious accumulation of the ion may occur with consequent toxic manifestations. Toxic levels may also be reached if salt intake is low, since lithium re-absorption will increase when sodium concentration in the tubules is low. On the other hand, serum levels of lithium are remarkably stable if kidney function and salt intake remain constant.

Until the serum level of lithium has been stabilized it should be checked weekly, but thereafter only monthly screening is needed. While the toxic level of lithium has been given as  $2.8 \text{ mmol} \cdot \text{L}$ , one would be well advised not to exceed  $2 \text{ mmol} \cdot \text{L}$  and indeed, in actual practice we have attempted to stay at or below  $1.5 \text{ mmol} \cdot \text{L}$ . Even with such safe doses, mild adverse effects may be seen. Most frequently, in our experience, these have been manifest as a fine tremor of the hands, fatigue and polyuria. These symptoms are only a nuisance, are usually well tolerated by patients grateful for relief of their headache and will disappear with reduction of dosage. Again, for reasons which are not at all clear, there appears to be some synergism between lithium carbonate and amitriptyline,<sup>12</sup> a tricyclic antidepressant. Thus we have been able to reduce the dose of lithium below that which may cause adverse effects and, by adding up to 75 mg of amitriptyline in each 24 hours, still to retain the same level of control of the cluster headache as had been obtained with a larger dose.

Depending upon the size of the patient we usually start treatment with lithium carbonate 300 mg twice or three times daily, increasing the dose gradually until either headaches are controlled or mild adverse reactions appear, at which point the dose is reduced to just below that level. It is of interest that, in prescribing lithium carbonate, the capsule form should be specified rather than the tablets. The capsule form is probably better absorbed than the tablets; in any case much larger doses are required to achieve the same plasma levels if tablets are used instead of capsules. Obviously great care must be taken that no changes are made from one to the other form as treatment progresses, so that plasma levels do not become either inadequate or excessive. Other adverse effects which usually disappear spontaneously after plasma levels have been stabilized are muscle weakness, nausea, vertigo and gastrointestinal discomfort. Occasionally nephrogenic diabetes insipidus with polydypsia is seen, necessitating discontinuance of lithium therapy.

Many questions remain unanswered. What is the nature of cluster headache? While some claim it to be of vascular origin,<sup>4,13</sup> others have shown this to be an unlikely pathogenesis.<sup>14</sup> How does lithium act in cluster headache and why does amitriptyline reinforce its effect and allow smaller doses to be used when, by itself, it has no influence on cluster headache?

While no claim can be made for lithium to be consistently and totally effective in cluster

headache, our experiences with this agent certainly corroborate the findings of those few investigators who have used this drug. Even when we have been unable to control the cephalgia completely, we have brought its intensity and frequency to a level where our patients have found it possible to function normally and without undue stress. After many years of unsuccessful or only partially successful treatment they have invariably found the relief most gratifying and this encourages us to publish this relatively small series so that others may benefit from our experience.

SUMMARY

Cluster headache is a form of unilateral headache which, in the past, has been very resistant to treatment. Lithium carbonate has been shown to be the only reliably effective treatment in this condition and, although only a few cases have so far been reported in the literature they have, with very few exceptions, been successful. Therefore we selected five patients who at one time or another had presented with cluster headache and who had no relief from conventional treatment, and treated them with lithium carbonate. This has been highly successful. Some patients who had suffered from the disease for many years have been completely or almost completely relieved of their affliction, while others have been markedly improved to the point where they can now function normally, both socially and professionally. The possible modes of action of lithium in this condition are discussed.

RÉSUMÉ

L'algie vasculaire de la face ou céphalée de Horton est une affection unilatérale qui était dans le passé rebelle à toute approche thérapeutique. Il a été démontré que le carbonate de lithium est le seul traitement efficace de cette affection, et bien que la littérature ne mentionne que peu de cas, ce traitement a été efficace à peu d'exceptions près. Nous avons choisi cinq malades souffrant de

cette maladie depuis plusieurs années et les avons traité au carbonate de lithium avec grand succès. Chez quelques uns la guérison a été complète ou presque complète alors que chez les autres l'amélioration a été suffisante pour un retour à une vie sociale et professionnelle normale. Les auteurs discutent du mécanisme possible d'action du lithium dans cette maladie.

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*Note:* Since going to press, five more patients have been similarly treated, all but one with equally gratifying results. In one patient attacks alternate between the left and right sides, a rare manifestation of cluster headache.