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Lithium Treatment of Chronic Cluster Headaches

By JULIAN LIEB and ARNOLD ZEFF

SUMMARY On the basis of reports of reduced MAO activity in migraine and cluster headaches and on a report that lithium carbonate activates MAO, the authors administered lithium carbonate to two patients whose cluster headaches had brought them to the point of contemplating suicide. Both patients responded quite dramatically. Case 1 has now been virtually free of headaches for over two years and Case 2 has been in remission for over twelve months.

Ekbom (1977) has defined chronic cluster headache as absence of remission periods, increased headache attack frequency, and diminished responsiveness to prophylactic drugs such as ergotamine, methysergide or steroids. The headaches occur with remarkable regularity and at night are related to REM sleep (Dexter, 1970).

Sandler (1974) reported that in migraine there is frequently a reduction in monoamine oxidase activity, and in his original series a patient in an acute phase of cluster headaches had the lowest MAO activity. Glover and associates (1977) have reported a highly significant decrease in platelet MAO activity during a migraine attack. Bockar and associates (1974) have reported that lithium increases platelet MAO activity. This finding, together with the awareness that lithium tends to ameliorate illnesses characterized by periodicity, led us to treat with lithium carbonate two patients whose cluster headaches had brought them to contemplate suicide. Case 1 has now been virtually free of headaches for over two years, and Case 2 has been in remission for over twelve months. A recent publication by Kudrow (1977), reporting marked improvement in 27 of 28 cluster patients treated with lithium, strongly suggests that lithium is indeed an effective drug in the treatment and prophylaxis of cluster headaches.

Case 1

C.H., a 37-year-old accountant, presented with a three year history of severe right-sided cluster headaches. The headaches started with a tingling sensation over the right carotid or the right temple and spread to the right orbit and sometimes to the right nostril. After ten minutes, the full-blown headache developed, which typically involved the right temple, the right eye with soreness and photosensitivity, and the right nostril with pain and discharge. Occasionally a stabbing pain developed in the area of the right carotid. After about half an hour, the headache would reach a climax and would then diminish over the next thirty minutes, either slowly or rapidly. The headaches typically lasted from 30 to 60 minutes and rarely extended beyond an hour. Occasionally, during the headache, Mr H. would break out in a profuse sweat accompanied by intense thirst. At worst the headaches occurred three times a day, on an average of four times a week. At one time, for a period of four months, C.H. awoke at 1.30 a.m. with a severe headache, and this was usually followed by a second headache between 7 and 8 a.m. When the headache occurred he could not lie still and would have to walk around. He obtained some analgesia from an icepack placed over the right carotid or the right temple. The longest headache-free interval over the three years was for a period of three months.

C.H.'s treatment history included ergotamine tartrate, meperidine, methysergide, propranolol and biofeedback. Ergotamine provided relief so long as it was taken at the first sign of a headache, but he became frightened of this medication, particularly when having to take 20 or more tablets a week. He viewed ergotamine as a symptomatic measure and felt the problem would return the following day. Methysergide provided only mild relief, and Mr H. discontinued it after a month. Propranolol was taken for a month without significant effect, and biofeedback had no effect.

Lithium carbonate was introduced at 300 mg twice a day (serum level 0.34 mEq/L) with no response. However, within two days of an increase to 1200 mg of lithium (serum level 0 76 mEq/L), C.H. reported a dramatic improvement in which his headaches disappeared save for an occasional feeling of 'sensitivity' along his right carotid. Up to the time of writing (27 months), he has experienced a solitary mild headache every two or three months.

Case 2

M.A., a 57-year-old auto parts manager, presented with a seven year history of cluster headaches. The headaches occurred daily, approximately once every three hours. They were described as sharp and throbbing and lasted from 20 to 30 minutes, with post-headache tenderness of the scalp. The headaches began deep in the right orbit or in the right temporal area, radiating to the vertex and the maxillary and mandibular areas. They were accompanied by unilateral tearing and rhinorrhoea. There was no history of prodromal nausea, vomiting, or scotomata. The patient had a history of headaches for periods of three to ten months a year, and the symptom-free intervals had gradually decreased each year, lasting from one to two months a year over the previous three years.

Several neurological and endocrine evaluations gave normal results. Unsuccessful therapeutic trials of medication included methysergide, Cafergot, steroids, propranolol, tricyclic antidepressants, phenothiazines, and a benzodiazepine. The patient had, in addition, proved refractory to histamine desensitization, tyramine-free diet, acupuncture, and psychoanalytic psychotherapy.

At the time of his current presentation, M.A. was taking ten grains of aspirin every three hours. He had been using aspirin as a self-prescribed remedy for the past several years. Occasionally the aspirin reduced the intensity of the headaches, but did not affect their frequency. Lithium carbonate was introduced at 600 mg per day, and gradual improvement was noted after a dosage of 900 mg per day was reached. The headaches completely disappeared ten days after the lithium dosage was increased to 1500 mg per day (blood level 1.15 mEq/L).

Because of mild neuromuscular side effects lithium was subsequently reduced to 900 mg per day (serum level 0.9 mEq/L) and M.A. remained completely headache-free for the following five months. At this stage, a family crisis erupted and M.A. developed a depressive episode which cleared with imipramine 100 mg per day. Three weeks after the initiation of imipramine the headaches began to return and progressed in severity and frequency until reaching a state similar to that before the initiation of lithium. The imipramine was discontinued, but despite manipulations of the lithium dosage the headaches could not be brought back under control and the patient left treatment.

After an interval of six months, M.A. returned and requested a second trial of lithium. His headache frequency was again one every three hours. Within six days of the reinstitution of lithium (900 mg, serum level 0.9 mEq/L), there was a dramatic decline in headache frequency to one headache a day or every other day. This has continued up to the time of writing (15 months).

Comments

For the purposes of the following discussion we will assume that migraine and cluster headaches share a similar if not identical pathophysiology, although we recognize that there is abundant controversy attached to this.

Herberg (1975) has speculated that the migraine syndrome is caused by a malfunction of the motivational, vegetative and autonomic mechanisms concentrated in the hypothalamus and adjacent areas of the brain stem. He proposes that migraine attacks originate as a disturbance of aminergic pathways, and drugs such as methysergide may owe their prophylactic properties to a facilitating effect on aminergic synapses rather than to a direct vasomotor action on the intracranial blood vessels.

Lithium carbonate is believed to produce alterations in brain indole and catecholamine metabolism, but its exact mechanism of action in this regard remains unclear. Kupfer and associates (1970) and Mendels and Chernik (1973) have reported that lithium administration results in a significant decrease in mean REM percentage and an increased latency to the first REM period. This mechanism may also be linked to the efficacy of lithium in chronic cluster headaches.

Since tricyclic antidepressants have been found to be effective in migraine prophylaxis (Couch, 1974, 1976), it is possible that M.A.'s relapse was due to the imipramine-lithium combination.

Tricyclic antidepressants, monoamine oxidase inhibitors and lithium carbonate have all been shown to be effective for some patients with vascular headaches (Ekbom, 1977; Couch, 1974, 1976; Anthony, 1969). There is evidence that these drugs alter MAO activity (Sandler, 1974; Glover, 1977; Bockar, 1974; Sullivan, 1977). As a transitory decrease in platelet MAO activity has been demonstrated during migraine attacks (Glover, 1977), tricyclic antidepressants, MAOIs and lithium carbonate could create their therapeutic effects in vascular headaches by stabilizing MAO.

Damasio and Beck (1978) have reported on 14 patients with migrainous attacks associated with thrombocytopenia and increased tendency to bruising. They hypothesize that migraine relates to abrupt changes in serotonin metabolism, which depends closely on the behaviour of platelets, the main serotonin reservoir in the blood. They further suggest that in idiopathic thrombocytopenic purpura, platelets sensitized

by an immunoglobulin release serotonin into the bloodstream before they are destroyed by the spleen. Since released free serotonin is rapidly metabolized and eliminated in the urine, further destruction of platelets would entail a reduction in total available serotonin. This would be compatible with evidence that blood serotonin rises before a migraine headache but is consistently low during the headache period. Taken in conjunction with the clinical evidence for the stabilization of manic-depressive illness and cluster headaches by lithium, this suggests that brain mitochondrial monoamine oxidase activity in manic-depressive illness, and platelet and/or brain monoamine oxidase activity in vascular headaches, are critical variables in these illnesses.

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