

Lithium treatment in cluster headache, review of literature

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ABSTRACT – Background: The pain, which is involved in Cluster Headache (CH), is excruciating and is probably one of the most painful conditions known to humans. In the early 70es it was found out that lithium could be used in treating this rare condition. Ekbohm produced his first report of using lithium successfully to treat five cases of CH and this was followed later by other studies, which showed the effectiveness of lithium in this condition.

Objective: In this article we reviewed the evidence for using lithium in CH. We discuss some issues including the duration, the dosage of lithium required and the short and long-term side effects, which are likely to occur. We also included the mechanism of action of lithium in treating this condition.

Methodology: We searched the Medline database from 1950 to date. We included all studies done in English, which were related to the use of lithium in cluster headache. We excluded all studies which were not in English and which included other types of headache.

Results and conclusions: We concluded that lithium is effective in both chronic and episodic forms of cluster Headache.

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Introduction

CH is a rare condition, which is characterized by severe explosive pain, which lasts for less than three hours and occurs mainly in males. There are two forms of CH namely the chronic and the episodic forms. In the chronic form, the attacks occur for more than one year without remission or with remission lasting less than 1 month. In the episodic form, the attacks occur in periods lasting 7 days to 1 year separated by pain free periods lasting 1 month or longer. The pain is strictly unilateral in the orbital, supra-orbital, and or temporal region and associated with ipsilateral cranial autonomic symptoms and signs such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, miosis, and low grade ptosis. Most patients are restless or agitated during an attack¹. Cluster Headache has been shown to be associated with dysfunction in the nervous system, notably with involvement of the hypothalamus. Attacks occur with remarkable regularity and are related to REM sleep. They are followed by refractoriness for few hours and tend to have a seasonal pattern².

Graham suggested that the effect of lithium on cluster headache may be, because this disorder shares several characteristics with manic depressive disease³.

Studies

Karl Ekblom did the first study when he treated 5 patients with CH (3 with chronic CH and 2 with episodic CH). Serum lithium level was maintained between 0.7 & 1.2 mEq/l. Lithium was found to be effective in all 5 patients².

In another study by Bussone *et al.*, 20 patients with a diagnosis of chronic CH were treated with lithium carbonate. The doses of lithium varied from 900mg to 2.2 gm/day. All patients improved rapidly on treatment and once treatment was stopped in some patients the headache returned within 36 hours⁴.

Later on, Kudrow treated a group of 32 patients suffering from chronic CH with lithium carbonate. The patients had previously tried different medications including methysergide, prednisone, and ergotamine without any result. Serum lithium levels were maintained lower than 1.2 mEq/l. 27 patients showed a dramatic improvement, whereas the therapy was found to be ineffective in 5 patients⁵.

Mathew undertook another clinical trial of lithium carbonate on 31 patients with CH (14 episodic, and 17 chronic). 80% of the patients responded to lithium and only 20% showed no improvement. Effectiveness of lithium was evident in less than a week after the initiation of treatment in those who responded. 55% of patients showed mild side effects. Treatment was stopped in one patient only because of intolerable side effects⁶.

In a study by Peatfield, 31 patients with CH were given lithium carbonate and the serum lithium levels were maintained at 0.6-0.69mmol/l. 14 patients showed a marked improvement in the first week, and 10 patients showed a lesser improvement⁷.

Ekblom gave a further contribution in 1981 when he conducted a study on 19 patients (8 with chronic CH and 11 with episodic CH). He tried lithium sulphate and lithium levels were maintained between 0.7 and 1.2 mmol/l. Immediate partial remission occurred in all chronic cases. In 4 cases with episodic CH lithium was continued for

several months which resulted in complete suppression of cluster periods. The rest of the patients with episodic CH had slight or no benefit⁸.

In a trial by Faustino Savoldi *et al.*, they included 90 CH patients (68 with episodic & 22 with chronic symptoms). In the 2nd week of lithium treatment over 80% of the patients with chronic CH improved by more than 90%. In the short term, some side effects occurred which were mild and tolerable. The doses of lithium varied from 600 to 1200 mg/day and plasma lithium levels varied from 0.3 to 0.8 m Eq/l. Of the 68 patients with episodic CH, about $\frac{3}{4}$ improved by > 60%. Mild side effects appeared in 18 cases (tremors, thirst, and insomnia). The plasma level varied from 0.3 to 0.7 m Eq/l⁹.

Manzoni *et al.* have investigated the short and long-term effects of administration of lithium carbonate (900 mg/day) in 90 patients with CH (68 episodic and 22 chronic). 50% of the patients with chronic CH (11 patients) showed a definite improvement, whereas, 50% had initial or partial improvement only. In 9 cases, cessation of lithium resulted in reappearance of symptoms. In the episodic group, 26 patients responded highly, 26 patients responded partially, and 16 cases were refractory. Reversible goitre developed in 3 cases after 1-3 years of treatment¹⁰.

A double blind study by Bussone *et al.* compared the effect of Lithium and Verapamil in treating CH. Showed that both Lithium and verapamil are effective in preventing Chronic CH. They involved 30 patients diagnosed with Chronic CH according to the International Headache Society criteria¹¹. Regarding efficacy, both drugs significantly improved Headache Index (HI), and Analgesic Consumption (AC). Verapamil showed > 50% reduction in HI and

58% in AC & Lithium showed > 37% and 58% respectively in the 1st week. Regarding Side effects, both drugs showed minor side effects (12% for verapamil and 29% for lithium)¹².

Steiner *et al.* conducted a double blind, placebo-controlled comparison of matched parallel groups of patients with episodic CH where treatment was slow release lithium carbonate, 800 mg/day, or placebo. Substantial improvement occurred in 8/13 (62% NS) on lithium and 6/14 (43%) on placebo and the trial was stopped because superiority of lithium could not be demonstrated¹³.

There are other case reports which showed the effectiveness of lithium carbonate in treating both forms of CH. Wyant & Ashenhurst reported five cases of patients who had a diagnosis of CH (4 chronic and 1 episodic). They tried lithium carbonate and later on added amitriptyline for patients with chronic CH and lithium carbonate only for the patient with episodic CH. Complete remission occurred in the patient with episodic CH and 1 patient with chronic CH. A significant improvement occurred in 3 patients with chronic CH¹⁴.

In 1978, Lieb & Zeff reported two cases with severe chronic CH to the extent that they had suicidal ideations. Both cases responded dramatically to lithium carbonate with serum levels of 0.76 - 1.15 mEq/l¹⁵.

Kilmek *et al.* used lithium carbonate to treat 15 patients with CH (8 chronic and 7 episodic). In all cases lithium serum level was maintained at 0.6-1.2 mmol/l. Disappearance of symptoms occurred in 5 patients (1 chronic and 4 episodic) and significant improvement occurred in 5 patients (4 chronic and 1 episodic). The treatment was ineffective in 5 patients (3 chronic and 2 episodic)¹⁶.

In an open trial, Damasio & Lyon tried lithium carbonate on 21 patients with CH (9 episodic, 12 chronic). 52.4% (n = 11) of patients showed absolute improvement, 23.8% (n = 5) showed partial improvement, and 23.8% (n = 5) did not improve or had temporary improvement only. Two patients had to discontinue treatment due to side effects¹⁷.

J M S Pearce reported 3 cases of episodic CH which responded dramatically to lithium carbonate at a dose of 250mg tds. No side effects were observed from lithium use¹⁸.

In 1980, Manzoni and Terzano tried lithium carbonate at gradually increased doses in 6 patients with chronic CH. The effective dose of lithium varied from 300 to 900mg/day¹⁹.

Zuddas *et al.* reported a case of chronic CH on haemodialysis treatment where lithium was used and led to a complete recovery²⁰.

Mechanism of action of lithium

Some trials have been undertaken in an attempt to understand how lithium works in patients with Cluster Headache.

Kupfer *et al.*²¹ and Mendels & Chernik²² reported that the immediate action of lithium in treating CH is related to its effect on REM sleep.

In another study by Medina *et al.*, it was found that lithium effect on CH is related to its effect on platelet serotonin and histamine levels²³.

It was also suggested that lithium action in CH can be attributed to its effect on opiate receptor affinity²⁴.

Giacovazzo *et al.* studied the relationship between genetic markers of patients with

CH and the therapeutic efficacy of lithium. In this study, 35 patients with episodic CH were involved. Lithium level was kept between 0.7 and 1.2 mEq/l. Two subgroups were identified (responders n = 21 and non responders n = 14). Responders displayed a higher frequency of the antigens HLA-B18 and HLA-A9 than did the non responders. The latter, on the other hand, showed a higher frequency of HLA-A1 than did the responders²⁵.

It was also found that lithium can correct the bilateral neuronal asymmetries which are related to the pathogenesis of CH²⁶.

In a study by De Bellaroché *et al.*, it was found that lithium restored the erythrocyte choline concentrations which were markedly reduced in patients with CH. This finding was consistent with a subsequent study which showed a decreased turnover in the erythrocyte phosphatidylcholine in CH sufferers^{27,28}.

Winter *et al.* suggested that the mechanism of action of lithium in CH lies behind its antiviral actions²⁹. This was based on the theory which suggests an association between CH and herpes simplex³⁰.

A study by G Chazot *et al.* showed the chronobiological effect of lithium in cluster headache. The result showed a decrease in melatonin amplitude at day 0 in the cluster group together with a rise in the cortisol. However in day 7 there was a delay in melatonin secretion with a shift but clear increase of the acrophase was observed. A decrease in cortisol level was also observed³¹.

The cyclic nature and hormonal alterations in CH indicate the involvement of the hypothalamus in the pathogenesis of this disorder. One possible mechanism of action of lithium is its effect on the serotonin level in the hypothalamus³².

Table I
Summary of studies of using lithium in Cluster Headache

Study	No. Of pts	Chronic CH	Episodic CH	Lithium Dosage and/or Level	Results	Side effects
Ekbm ²	5	3	2	0.7-1.2 mEq/l	100% improved	Nil reported
Kudrow ⁵	32	32	0	<1.2 mEq/l	27 patients improved dramatically. 5 patients did not respond.	4 patients discontinued because of severe side effects (headache, abdominal pain, and vomiting).
Mathew ⁶	31	17	14	Up to 900mg/d Level:0.5-1.2mEq/l	80% showed improvement (>90% improvement in 55%, 60-90% improvement in 10%, 25-60% improvement in 15%). 20% showed no improvement	55% of patients showed mild side effects (tremors, nausea, diarrhea, and abdominal discomfort). 1 patient discontinued due to intolerable side effects (disabling lethargy).
Peatfield ⁷	31	4	27	800-1600 mg nocte Level:0.60-0.69 mmol/l	Marked improvement- 14 patients. Lesser improvement-10 patients. No improvement-7 patients.	Intractable vomiting induced in 2 cases.
Ekbm ⁸	19	8	11	0.7-1.2mmol/l	8 Chronic cases showed immediate partial remission. 7 episodic patients showed slight or no effect. 4 episodic cases showed complete remission with long term treatment	3 patients in the chronic group reported slight diarrhea, tremor, and increased thirst. 3 patients in the episodic group reported tiredness, tremor, vertigo, diarrhea, and increased thirst.
Savoldi ⁹	90	22	68	600-1200 Levels: 0.3-0.8mEq/l.	More than 80% of chronic cases improved >90%. 75% of episodic cases improved >60%.	Mild tolerable side effects in 18 episodic cases (tremors, thirst, and insomnia). Mild tolerable side effect in 7 chronic cases (tremor, diarrhea, abdominal pain, olfactory hallucinations, insomnia, vertigo, and increased thirst). Long term side effects included reversible goitre.
Manzoni et al. ¹⁰	90	22	68	900mg/d	Constant improvement in 11 chronic cases. High response in 26 episodic cases.	Mild side effects (tremor, increased thirst, insomnia, diarrhea, lethargy, diffuse headache, abdominal pain, olfactory hallucination, and vertigo). 3 cases developed euthyroid goitre after 1-3 years of treatment which disappeared after stopping lithium.
Bussone ¹²	30	30	0	900mg/d	>37% reduction in HI and 58% reduction in AC	29% of patients developed minor side effects (gastrointestinal complaints, behavioural changes, tremor, and increased diuresis).

Table I (continue)

Study	No. Of pts	Chronic CH	Episodic CH	Lithium Dosage and/or Level	Results	Side effects
Steiner ¹³	13	0	13	800mg/d 0.5-0.6mmol/l	62%;NS 8 cases) showed substantial improvement	Only minor side effects reported (polyurea reported in 5 cases).
Wyant <i>et al.</i> ¹⁴	5	4	1	600mg/d in 1 case. Levels: 1.14 and 1.28 in 2 cases.	Complete remission in 2 cases (1episodic and 1 chronic). Significant improvement in 3 cases.	Nil reported.
Lieb & Zeff ¹⁵	2	2	0	Doses: 1200& 1500mg/d. Levels:0.76-1.15mEq/l	Both cases improved dramatically.	Mild neuromuscular side effects in 1 case.
Kilmeek <i>et al.</i> ¹⁶	15	8	7	Doses: 750-1500 mg/d. Levels:0.6-1.2 mmol/l	Remission in 5 cases (1 chronic and 4 episodic). Significant improvement in 5 patients (4 chronic&1 episodic) No improvement in 5 cases (3 chronic&2 episodic).	1 patient developed intolerable side effects and treatment was discontinued. No other side effects reported.
Bussonne <i>et al.</i> ⁴	20	20	0	900mg-2.2gm/d	16 cases improved rapidly with no further crisis while on treatment for 2-24 weeks. 4 cases improved but not completely.	1 patient reported gastric disturbances and headache while on a high dose.
Damasio & Lyon ⁷	21	12	9	Doses: 600-1500 mg/day. Level:0.38-1.14 mg/ml	Absolute improvement.-11 patients. Partial improvement-5 patients. No improvement-5 patients.	No serious side effects were noted but 2 patients had to discontinue treatment due to side effects (diarrhea, polyurea, polydypsia, dizziness, and unsteadiness).
Pearce ¹⁸	3	0	3	250mg tds	All patients responded dramatically	Nil reported.
Manzoni & Terzano ¹⁹	6	6	0	300mg/d in 1 case. 600mg/d in 3 cases. 900mg/d in 2 cases	90% improvement in all cases.	Nil reported.
Zuddas <i>et al.</i> ²⁰	1	1	0	300mg/d during dialysis 150mg/d during non dialysis.	Complete recovery when lithium level reached 0.46 mmol/l.	Nil reported.

Discussion

We concluded from our review that lithium can be effective in both types of cluster headache but, perhaps, the evidence of its effectiveness in episodic forms is rather controversial. Some authors found that there is a decrease in the effectiveness of lithium after prolonged use in this condition. This may be due to tolerance or lack of compliance for one reason or another. There is a controversy regarding the required dose of lithium in patients with CH and some authors required higher doses to reach a plasma level between 0.7-1.2 mmol/l. Others, on the other hand, found that low doses of lithium with plasma levels between 0.4-1.0 mmol/l should be adequate for this condition.

In the short term the side effects of lithium are generally tolerable and they are mainly in the form of fine hand tremors, polyurea, and polydypsia. In the long term, hypothyroid goitre and renal impairment may develop. Hypothyroidism secondary to long-term lithium treatment can be treated and should not be an indication to stop lithium in stable clients. It is important that patients be well informed as to the needs for periodic lithium blood level determinations and the adverse as well as the beneficial effects of the drug.

It should be noted that with exception of the two studies done by Bussone *et al.*¹², and Steiner *et al.*¹³, results have been derived solely from open clinical trials.

Although there are different theories behind the mechanism of action of lithium in treating CH, however, it remains unclear to how exactly it works and produces its rapid effect in this condition.

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