REVIEW ARTICLE

Lithium-responsive headaches

Cefaleias lítio-responsivas

Raimundo Pereira da Silva Neto[1], Kelson James Almeida[2]

[1]Neurologista e Membro da Sociedade Brasileira de Cefaleia
[2]Residente de Neurologia do HC-USP
Centro de Neurologia e Cefaleia do Piauí - Teresina PI, Brasil

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RESUMO

Introduction: Lithium-responsive headaches are primary and they have beginning nocturnal or on awakening. They are classified in three groups: Nocturnal Migraine, Cluster Headache, and Hypnic Headache. All three types show a positive therapeutic response to lithium and the average dose is from 300 to 900 mg at bedtime. **Objective:** To review the headaches that have nocturnal or on awakening beginnings and those which demonstrate a therapeutic response to lithium. **Method:** We reviewed the literature on lithium and its historical and pharmacological aspects, and its use in the treatment of nocturnal headaches. **Conclusion:** Lithium is an efficient drug in the treatment of nocturnal headache and headache on awakening.

Palavras-chave: Nocturnal migraine; cluster headache; hypnic headache; lithium-responsive headaches.

ABSTRACT

Introdução: As cefaleias lítio-responsivas são primárias e se caracterizam por seu início noturno ou ao despertar. São divididas em três grupos: migrânea noturna, cefaleia em salvas e cefaleia hípnica. Todas têm boa resposta terapêutica ao lítio e a dose varia de 300 a 900 mg/dia. **Objetivo**: Revisar as cefaleias que têm início durante o sono ou ao despertar e que respondem ao lítio. **Método:** Foi revisada a literatura sobre o lítio quanto ao seu histórico, sua farmacologia e a sua utilização clínica no tratamento das cefaleias noturnas. **Conclusão:** O lítio é uma medicação eficaz no tratamento da cefaleia noturna e ao acordar.

Key words: Migrânea noturna; cefaleia em salvas; cefaleia hípnica; cefaleias lítio-responsivas.

INTRODUCTION

Nocturnal headaches (Table 1) are generated during sleep and occur either at dawn or awaken the patient during the night.[1-7] There is a temporal relationship between the nocturnal headache attacks and the period of REM sleep. These headaches are divided into primary (nocturnal migraine, cluster headache and hypnic headache) and secondary (attributed to giant-cell arteritis, intracranial hypertension secondary to hydrocephalus or intracranial neoplasia and sleep apnea headache). All primary headaches respond to therapy using lithium carbonate and therefore are referred to as lithium-responsive, while the treatment of secondary headaches is based on the removal of their cause.

LITHIUM IN HEADACHES

Lithium (from the Greek *lithos*, stone) is a chemical element represented by the symbol Li, discovered by Johan August Arfwedson in 1817 through minerals derived from a petalite mine on the island of Utö (Sweden). The principal minerals from which lithium is extracted are lepidolite, petalite, spodumine and amblygonite. The name lithium was given due to the fact that it had been found inside a mineral, even though it was later found in plant ashes as well.

Lithium is found in diverse forms within nature, such as: salts, chlorides, bromides, stearate, hydroxides, etc.

Table 1. Nocturnal Headaches

Primary Headaches
Nocturnal Migraine
Cluster Headache
Hypnic Headache
Secondary Headaches
Attributed to giant-cell arteritis
Attributed to intracranial hypertension secondary to hydrocephalus
Attributed to intracranial neoplasia
Sleep apnea headache

Only the lithium salts are used in medicine, particularly lithium carbonate (Li_2CO_3). Initially classified as an anti-psychotic, but today it is used for its regulating effects on mood, anti-mania and, secondarily, as an anti-depressant.

The activating mechanism of lithium is not well elucidated, however it is known to be effective in pathologies of clinical evolution, inhibiting the synthesis of prostaglandin and the action of the prolactin, acting on the monoamine, the cyclic AMP, the platelet and sleep. Lithium establishes and increases the serotoninergic transmission in the central nervous system, particularly in the hippocampus. Due to this, it has been used in the treatment of nocturnal headaches. According to Silva Neto *et al.*,[8] lithium is an effective medication in the treatment of nocturnal and awakening headaches as well as nightmares.

Lithium is rapidly absorbed by the gastrointestinal tract and the plasmatic concentration reaches its peak within two to four hours after ingestion. Lithium slowly crosses the blood-brain barrier. Ninety-five percent (95%) of the drug is excreted via urine in a rapid phase and in another slower phase, which may take as long as 14 days. Lithium should not be used concurrently with a hyposodic diet or with diuretics that induce the loss of sodium, given that the depletion of sodium provokes intracellular retention of lithium.

The average dose is from 300 mg two to three times daily, taken orally, aiming to maintain a plasmatic concentration between 0.4 and 0.8 mEq/l. The periodic control of the serum level should be given.

There are diverse collateral effects to various organs, some of them quite worrisome:

1. Neurotoxicity: drowsiness, mental confusion, lethargy, clouded vision, shaking of the extremities, cramping, dizziness, nystagmus, ataxia, extrapyramidal signs, and convulsions;

2. Thyroid: hypothyroidism (10 times more frequent in women) in 5% of the cases and painless increase in the thyroid (reversible with the suspension of the use of the drug). Doses of TSH, T3 and T4 should be given every six months;

3. Renal: edema and sodium retention in the initial phase of treatment, polyuria, polydipsia, and insipid diabetes by hormonal anti-diuretic blockage at the renal tube level;

4. Hematological: leukocytosis for polymorpho-nuclears;

5. Cardiac: tachycardia and narrowing of the T wave and dysfunction of the sinus nodule;

6. Dermatalogical: cutaneous ulcers, psoriasis, hair loss, and acne-like eruptions;

7. Gastrointestinal: nausea, vomiting, diarrhea, and abdominal pains;

8. Pregnancy: there are registered occurrences of new-borns of mothers using lithium that acquire depression of the central nervous system, hypotonia, neonatal goiter, and cardiac malformations, especially Ebstein's anomaly.

THE PRIMARY NOCTURNAL HEADACHES

Nocturnal Migraine

A migraine without aura where all of the attacks begin during the night or upon awakening.[1] Still has not been sufficiently validated by scientific studies. Overall, the experience of specialists suggests the existence of a primary headache that arises either during sleep or upon awakening and fulfills the diagnostic criteria for migraine and not for other primary headaches. Additional scientific evidence is required in order to formally accept and include in the next international classification of headaches.

According to Edgard Raffaelli (personal conversation), similar to the menstrual headache, nocturnal migraine do not respond to habitual prophylactic treatments for migraine, suggesting the existence of at least three different neurotransmission systems.

Due to the use of lithium in pathologies having a cyclical evolution, testing was begun on nocturnal migraine. These patients have had an absolute therapeutic response to lithium carbonate, at a daily dosage of 300 to 900 mg/day in the form of a singular night-time dosage.[8,9]

Cluster Headache

A primary headache from the trigeminal autonomic cephalalgias group that presents certain peculiarities such

as: excruciating pain, short-term attacks, evident circadian rhythm, regularity, and autonomic disturbances.[10]

The classification of headaches of the International Headache Society (IHS-2004)[11] describes the cluster headache as attacks of intense pain, strictly unilateral, located in the orbital, supraorbital or temporal region, lasting from 15 to 180 minutes and occurring from once every other day to eight times daily. This headache occurs in association with one or more of the following aspects, all of which are ipsilateral to the pain: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, facial and forehead sweating, miosis, ptosis, and eyelid edema.

Some nuances not described in the classification of headaches are observed in clinical practice such as the time at which the attacks occur. It has been observed that the attacks consistently occur at the same time of day in a significant number of patients. According to Lance, the occurrence of a circadian rhythm will be present in 80%-85% of the cases and the nocturnal attacks will be more frequent, in the range of 50-60% of the crises, approximately 90 minutes after the patient falls asleep. Dexter and Riley[6] reference their findings that seven in nine crises of cluster headaches occur during REM sleep. Polysomnographic study shows that awakening with a headache occurs more frequently during the period of REM sleep, during the third and fourth stages.

Lithium was indicated as the treatment for cluster headache by Ekbon in 1974. It is used in the treatment of episodic nocturnal cluster headache attacks at the dosage of 300 to 600 mg/day given orally at night in a single dose. For chronic cases a dosage of 300 mg two-three times daily is recommended.[12]

Hypnic Headache

A primary headache that awakens the patient, also known as an "alarm clock headache" or "clockwise headache" and characteristically affecting the middle-aged and elderly.[13]

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The hypnic headache was described originally by Raskin in 1988 through a study of six subjects (5 men and one woman), with ranging from 65-77 years of age, with headache attacks that awakened them (in two of them always after dream) and lasted from 30 to 60 minutes. In three of the patients the pain was pulsing. Only two of those studied reported cases of migraine in the past, one with and the other without aura. None of the patients presented autonomic disturbances that suggest cluster headache and all of them reported bilateral pain.

Through the initial description by Raskin, various cases were described in literature,[14,15] culminating in its inclusion in the International Classification of Headaches

Hypnic headache is defined by the International Headache Society[11] as a dull headache that always awakens the patient and that fulfills the following diagnostic criteria: appears only during sleep and awakens the patient, happens more than 15 times per month, last 15 minutes or more after awakening and occurs for the first time after 50 years of age. There is an absence of autonomic signs and there will be no more than one of the following symptoms: nausea, vomiting, photophobia or phonophobia. It is not attributed to any other disturbance or disorder.

Various studies have demonstrated that lithium carbonate was the most effective treatment in a variety of related cases.[4,14,15] The dosage used varied from 300 to 600 mg/day in a single dose, always at night upon going to bed.

CONCLUSION

Lithium has been shown to be a good therapeutic response to all primary headaches that present themselves during the night or upon awakening.

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Correspondência
Dr. Raimundo Pereira da Silva Neto
Centro de Neurologia e Cefaleia do Piauí
Rua São Pedro, 2071 - Centro
Ed. Raimundo Martins - Salas 303/304
64001-260 - Teresina-PI - Brasil
Tel./fax: + 55 86 3221.9000
E-mail: neurocefaleia@terra.com.br