CLINICAL CASE

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ABSTRACT

An anti-suicide effect has been well documented in prolonged lithium treatments, with high-quality evidence in bipolar disorder and unipolar depression, shown to be significantly superior to other mood stabilizers, with a 50-80% of reduction in suicide risk.

We illustrate the case of a 70-year-old man who was admitted to our unit for attempted suicide by hanging after discontinuation of lithium treatment due to the detection of renal damage. Clinical stability had been maintained since the onset of the disease with a dose of 1200 mg/d, which was then reduced to 600 mg/d, obtaining maintained infratherapeutic levels of lithium of 0.32-0.34 mEq/L, psychopathological stability persisting for several more years.

Subsequently, progressive lithium withdrawal was performed over a 6-month period, which conveys depressive decompensation with delusion of harm approximately one month after complete withdrawal, without any improvement under antidepressant and antipsychotic treatments, culminating in attempted suicide aforementioned.

Notwithstanding an evident mood stabilizing and anti-suicide effects, and the fact that one third of the patients with bipolar disorder are considered excellent responders to lithium monotherapy, with complete remission of affective relapses, its use has declined in different countries for the last decades in favor of other drugs with a mood stabilizing effect.

Nevertheless, lithium is effective and safe in general. By performing adequate controls, its benefits often outweigh the risks. Overall, it is recommended to maintain it even in patients with a partial affective response, especially before a high suicide risk.

Keywords. Bipolar disorder, lithium, antisuicidal effect, suicide.

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EFECTO ANTISUICIDA DEL LITIO A DOSIS INFRATERAPÉUTICA, A PROPÓSITO DE UN CASO

RESUMEN

Ha sido bien documentado un efecto antisuicida en tratamientos prolongados con Litio, con evidencias de alta calidad en trastorno bipolar y depresión unipolar, demostrado significativamente superior al de otros estabilizadores del ánimo, con reducción del riesgo suicida en un 50-80%.

Presentamos el caso de un varón de 70 años que ingresa en nuestra unidad por intento de ahorcamiento tras suspensión del tratamiento con Litio debido a detección de daño renal. Se había mantenido estabilidad clínica desde el debut de la enfermedad con dosis de 1200 mg/d, decidiéndose entonces reducción hasta 600 mg/d, obteniéndose litemias mantenidas en niveles infraterapéuticos de 0,32-0,34 mEq/L, persistiendo estabilidad psicopatológica varios años más. Posteriormente, se realiza retirada progresiva de Litio en un periodo de 6 meses, produciéndose aproximadamente al mes de la retirada completa descompensación depresiva con delirio de perjuicio, sin mejoría con pauta antidepresiva y antipsicótica; que culmina en el gesto autolítico mencionado.

A pesar de un evidente efecto estabilizador del ánimo, antisuicida y del hecho de que un tercio de pacientes con trastorno bipolar se consideran excelentes respondedores a Litio en monoterapia, con remisión completa de recaídas afectivas; su uso ha declinado en distintos países durante las últimas décadas, en favor de otros fármacos con efecto estabilizador del ánimo.

A pesar de ello, en general el Litio es eficaz y seguro. Realizando controles adecuados, sus beneficios suelen superar a los riesgos. En general, se recomienda mantenerlo incluso en pacientes con respuesta afectiva parcial, especialmente ante riesgo suicida elevado.

Palabras clave. Trastorno bipolar, litio, efecto antisuicida, suicidio.

INTRODUCTION

Lithium is a first-line mood stabilizing drug to prevent affective relapses in bipolar disorder, also indicated for resistant depression[1-4].

There is evidence of a significantly higher risk of suicide in individuals with mood disorders[5, 6], with 25-50% of patients with bipolar disorder having a medical history of at least one suicide attempt[4] and an estimated annual suicide rate of 4%[7,8].

The anti-suicide effect of lithium has been well documented in treatments lasting at least 3 months[8], with high-quality evidence in bipolar disorder and unipolar depression, showing that it is significantly superior to that of other mood stabilizers[4, 7, 9-19], with suicide risk reduction of 50-80%[20, 21]. With more limited conclusions, some studies also conclude that this effect is exerted rapidly after the beginning of treatment[8] and there is also evidence in other diagnoses, such as schizoaffective disorder, dysthymia or rapid cycling bipolar disorder[21]. Regarding its mechanism of anti-suicide action, the reduction of impulsivity and aggressiveness[22], proinflammatory theories[23] or the reduction of testosterone are contemplated as hypothesis, the latter being in line with some studies that demonstrate the anti-suicide effect of lithium in men[6, 14, 18, 24].

Studies from different countries reveal an anti-suicide effect of exposure to minimum doses of lithium naturally present in drinking water[3, 13, 18, 25, 26], what involves plasma levels of 0.001 to 0.04 mEq/L[14], much lower than those ones considered therapeutic. Several studies establish 30-31 microg/L as the minimum dose that has demonstrated an anti-suicide effect[24, 27]. Proposals have been supported to supplement drinking water with lithium in certain geographical areas[3] to attempt to reduce suicide rates in the general population[6].

CASE REPORT

Here is the case of a 70-year-old man who was admitted to our psychiatry unit due to a suicide attempt after suspending treatment with lithium.

He shows no signs of drug allergies as somatic history. He suffers from arterial hypertension in treatment with Lecarnidipine 20 mg/d and chronic renal failure in follow-up by nephrology.

Regarding his mental health background, he had been diagnosed with bipolar disorder at the onset of approximately at the age of 40, in regular outpatient psychiatric monitoring, with good compliance with the treatment prescribed for years. There have been two psychiatric admissions at the onset of mental illness for maniac episodes.

He does not present a psychiatric family history or toxic habits.

Psychopathological stability has been preserved for more than 25 years under treatment with lithium at a dose of 1200 mg/d in combination with Clotiapine 40 mg taken in the evening.

In evaluation by the nephrology service, moderate chronic renal failure was described due to stable chronic interstitial nephropathy with creatinine levels around 1.60 mg/dl. Therefore, it was decided to reduce the lithium dose progressively to 600 mg/d, obtaining from that moment lithium levels maintained at subtherapeutic levels of 0.32-0.34 mEq/L, with psychopathological stability persisting for more than two years.

As the nephrology service determines that lithium could be promoting kidney damage, a and therefore they recommend avoiding it as much as possible, progressive withdrawal of lithium is carried out over 6 months, which involves a decompensation to the depressive pole approximately one month after complete withdrawal, together with hypothymia, apathy, anhedonia, global insomnia, irritability, negativism, and recurrent death ideas. In addition, delirium of prejudice reappears. He shows little improvement despite the establishment of Sertraline 100 mg/d and Paliperidone 6 mg/d.

In this way, the patient committed an impulsive attempt of hanging in the doorway of his home with no anticipation of rescue. He was found unconscious by his brother, a fact that motivated his admission to our hospitalization unit.

A few days after admission, a maniac shift is observed, including hyperthymic attitude, megalomaniacal verbalizations and disinhibited attitudes towards female patients.

During hospitalization, lasting a total of 22 days, it was decided to change the stabilizer treatment to prolonged-release valproate, reaching a dose of 800 mg/day, obtaining valproemia of 55.80 µg/ml, with good tolerance. In addition, Sertraline was suspended, maintaining Clotiapine, Paliperidone and antihypertensive treatment. Almost at the beginning of admission, the suicidal ideation cedes, subsequently reaching euthymia. Progressively delusional ideation acquires an encapsulated character and insomnia is corrected.

With regard to complementary tests, blood tests are performed, highlighting a Creatinine value of 1.55 mg/dl, with an Estimated Glomerular Filtration rate of 44.7 ml/min/1.73m2, with no other pathological findings to note in the blood count, coagulation, biochemistry and systematic urine.

Table 1 specifies the timing of the lithium dose adjustments carried out in relation to the renal function values.

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Table 1 Timeline of lithium dose adjustments carried out in relation to lithium levels and renal function figures.

PRIOR TIME UNTIL ADMISSION	LITHIUM DOSE (mg/d)	LITHIUM LEVEL (mEq/L)	CREATININE LEVEL
3 years and 2 months	1200	¿?	1.64
2 years and 3 months	800	¿?	1.50
1 year and 9 months	600	0.34	¿?
6 months	600	0.32	1.75
3 months	400	¿?	¿?

DISCUSSION

The serum concentration of lithium necessary to induce an anti-suicide effect remains unclear[4]. This effect has been documented at levels between 0.5 and 1 mmol/L[3, 4], with some researchers advocating that it could be achieved with lower doses[6,10], as occurred in the case of our patient.

Although in our case the suicide attempt occurs in relation to a depressive relapse, the anti-suicide properties of lithium do not seem to be exclusively related to its mood stabilizing effect, having been shown a reduction of suicide attempts in patients in whom it did not present efficacy on mood symptoms[4 ,6, 22].

Although the suicide attempt occurs after slowly progressive withdrawal of lithium treatment in the case presented, the increased risk of suicide described after discontinuation[3, 15, 22] occurs especially when it is carried out abruptly[7].

Regarding mood-stabilizing drugs, although lithium is the only one that has firmly demonstrated an anti-suicide effect[20] and the findings concerning the rest are inconsistent[7], certain studies affirm that valproate or carbamazepine could also have it in patients with bipolar disorder[8, 17]. Therefore, we decided ti choose Valproate. As per antipsychotics, although there is some evidence of reduction in suicidal ideation or behavior in patients with affective disorders treated with atypical ones, specifically Sertindole, Olanzapine and Risperidone, it should be noted that Clozapine is the only one that has been shown to reduce the risk of suicide in patients diagnosed with schizophrenia[7] unquestionably. Although evidence with anxiolytics and other antidepressants is inconsistent[7], studies with Ketamine suggest promising results in terms of reducing suicidal thoughts in the short term[17, 19].

It should be pointed out that, despite the obvious mood stabilizing and anti-suicide effects of lithium, and the fact that, as in the case presented, one-third of the patients with bipolar disorder are considered excellent responders to lithium monotherapy, with complete remission complete of affective relapses[28]; its use has diminished in different countries for the last decades in favor of other drugs with mood-stabilizing effect[2, 3, 16, 29, 30]. This fact is probably related to a predominance of suboptimal responses, the need for regular blood monitoring, the perception of greater toxicity, and the need for prolonged trials to determine their response.[2, 31]. Regardless, lithium is generally effective and safe, and the benefits often outweigh the risks, especially if adequate controls are performed[4].

Although in our case the risk-benefit assessment was complex, in general it is recommended, whenever possible, to maintain treatment with lithium, even in patients with partial affective response, especially in cases of high suicidal risk[4].

Conflicts of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Mohammed T. Abou-Saleh, Bruno Muller-Oerlinghausen, Alec J. Coppen. Lithium in the episode and suicide prophylaxis and in augmenting strategies in patients with unipolar depression. Int J Bipolar Disord. 2017;5:11. DOI 10.1186/s40345-017-0080-x.
2. David A Cousins, Letizia Squarcina, Fawzi Boumezbeur, Allan H Young, Frank Bellivier. Lithium: past, present, and future. Lancet Psychiatry. 2020;7:222-224.
3. Janusz K. Rybakowski. Lithium - past, present, future, International Journal of Psychiatry in Clinical Practice. 2020;24(4):330-340. DOI: 10.1080/13651501.2020.1775855.
4. Simrat Kaur Sarai, Hema Madhuri Mekala, Steven Lippmann. Lithium Suicide Prevention: A Brief Review and Reminder. Innov Clin Neurosci. 2018;15(11–12):30-32.
5. Alina Wilkowska, Mariusz S. Wiglusz, Wiesław J. Cubała. Clozapine in Treatment-Resistant Bipolar Disorder With Suicidality. Three Case Reports. Frontiers in Psychiatry. 2019;10(520). DOI: 10.3389/fpsyt.2019.00520.
6. Fateme Barjasteh-Askari, Mojtaba Davoudi, Homayoun Amini, Mohammad Ghorbani, Mehdi Yaseri, Masoud Yunesian, Amir Hossein Mahvi*, David Lester. Relationship between suicide mortality and lithium in

drinking water: A systematic review and meta-analysis. Journal of Affective Disorders. 2020;264:234–241.
7. Leonardo Tondo, Ross J. Baldessarini. Suicidal Behavior in Mood Disorders: Response to Pharmacological Treatment. Curr Psychiatry Rep. 2016;18:88. DOI 10.1007/s11920-016-0715-0.
8. Chia-Jui Tsai, ChinCheng, Po-HanChou, Ching-HengLin, MelvinG.McInnis, Chia-Li Chang, Tsuo-HungLan. The rapid suicide protection of mood stabilizers on patients with bipolar disorder: A nationwide observational cohort study in Taiwan. Journal of Affective Disorders. 2016;196:71-77.
9. Caley CF, Perriello E, Golden J. Antiepileptic drugs and suicide-related outcomes in bipolar disorder: A descriptive review of published data. Ment Health Clinician. 2018;8(3):138-47. DOI: 10.9740/mhc.2018.05.138.
10. Tondo L, Baldessarini RJ. Antisuicidal Effects in Mood Disorders: Are They Unique to Lithium?. Pharmacopsychiatry. 2018; 51(05): 177-188. DOI: 10.1055/a-0596-7853.
11. Miller JN, Black DW. Bipolar Disorder and Suicide: a Review. Curr Psychiatry Rep. 2020;22(6):1-10. DOI: 10.1007/s11920-020-1130-0.
12. König D, Baumgartner J, Blüml V, Heerlein A, Téllez C, Baus N, Kapusta ND. Einfluss von natürlichen Lithiumsalzvorkommen auf die Suizidmortalität in Chile 2000–2009: Eine geographische Analyse. Neuropsychiatr. 2017;31:70-76. DOI: 10.1007/s40211-017-0222-5.
13. Eric E. Brown, Philip Gerretsen, Bruce Pollock, Ariel Graff-Guerrero. Psychiatric benefits of lithium in water supplies may be due to protection from the neurotoxicity of lead exposure. Medical Hypotheses. 2018;115:94–102.
14. Masayuki Kanehisa, Takeshi Terao, Ippei Shiotsuki, Keiko Kurosawa, Ryuichi Takenaka, Teruo Sakamoto, Osamu Shigemitsu, Nobuyoshi Ishii, Koji Hatano, Hirofumi Hirakawa. Serum lithium levels and suicide attempts: a case-controlled comparison in lithium therapy-naive individuals. Psychopharmacology. 2017;234:3335–3342. DOI 10.1007/s00213-017-4729-z.
15. Jie Song, Ph.D., Arvid Sjölander, Ph.D., Erik Joas, M.S., Sarah E. Bergen, Ph.D., Bo Runeson, M.D., Ph.D., Henrik Larsson, Ph.D., Mikael Landén, M.D., Ph.D., Paul Lichtenstein, Ph.D. Suicidal Behavior During Lithium and Valproate Treatment: A Within-Individual 8-Year Prospective Study of 50.000 Patients With Bipolar Disorder. Am J Psychiatry. 2017;174 (8):795-802. DOI: 10.1176/appi.ajp.2017.16050542.
16. Diego Antolin-Concha, Markku Lahteenvuo, Pia Vattulainen, Antti Tanskanen, Heidi Taipale, Eduard Vieta, Jari Tiihonen. Suicide mortality and use of psychotropic drugs in patients hospitalized due to bipolar disorder: A Finnish nationwide cohort study. Journal of Affective Disorders. 2020;277:885-892.
17. Gil Zalsman, Keith Hawton, Danuta Wasserman, Kees van Heeringen, Ella Arensman, Marco Sarchiapone, Vladimir Carli, Cyril Höschl, Ran Barzilay, Judit Balazs, György Purebl, Jean Pierre Kahn, Pilar Alejandra Sáiz, Cendrine Bursztein Lipsicas, Julio Bobes, Doina Cozman, Ulrich Hegerl, Joseph Zohar. Suicide prevention strategies revisited: 10-year systematic review. Lancet Psychiatry. 2016;3:646-59. DOI: 10.1016/S2215-0366(16)30030-X.
18. Ippei Shiotsuki, TakeshiTerao, NobuyoshiIshii, ShouheiTakeuchi, YoshikiKuroda, KentaroKohno, YoshinoriMizokami, KojiHatano, SanshiTanabe, MasayukiKanehisa, NoboruIwata, ShinyaMatusda. Trace lithium is inversely associated with male suicide after adjustment of climatic factors. Journal of Affective Disorders. 2016;189:282-26.
19. Kristen E. D'Anci, PhD; Stacey Uhl, MS; Gina Giradi, MS; and Constance Martin, BA. Treatments for the Prevention and Management of Suicide. A Systematic Review. Ann Intern Med. 2019;171(5):334-352. DOI:10.7326/M19-0869.
20. Prashant Tibrewal, Tracy Ng, Tarun Bastiampillai, Rohan Dhillon, Dong Hoon Koh, Sandip Kulkarni. Why is lithium use declining? Asian Journal of Psychiatry. 2019; 43:219-220.
21. Nestor D. Kapusta, Daniel König. Naturally ocurring low-dose lithium in drinking water. J Clin Psychiatry. 2015;76:3.
22. L. Del Matto, M. Muscas, A. Murru, N. Verdolini, G. Anmella, G. Fico, F. Corponi, A.F. Carvalho, L. Samalin, B. Carpiniello, A. Fagiolini, E. Vieta, I. Pacchiarotti. Lithium and suicide prevention in mood disorders and in the general population: A systematic review. Neuroscience and Biobehavioral Reviews. 2020;116:142-153.
23. Wendy K. Adams, Dominique L. Levesque, Paul J. Cocker, Sukhbir Kaur, Tamara S. Bodnar, Allan H. Young, Catharine A. Winstanley. Decreased motor impulsivity following chronic lithium treatment in male rats is associated with reduced levels of pro-inflammatory cytokines in the orbitofrontal cortex. Brain, Behavior and Immunity. 2020:89:339–349.
24. Tsuyoshi Kugimiya, Nobuyoshi Ishii, Kentaro Kohno, Masayuki Kanehisa, Koji Hatano, Hirofumi Hirakawa, Takeshi Terao. Lithium in drinking water and suicide prevention: The largest nationwide epidemiological study from Japan. Bipolar Disorders. 2020;00:1–8. DOI: 10.1111/bdi.12983.
25. Pedro Oliveira, Joana Zagalo, Nuno Madeira, Orquídia Neves. Lithium in Public Drinking Water and Suicide Mortality in Portugal: Initial Approach. Acta Med Port. 2019;32(1):47-52.

Actas Esp Psiquiatr 2022;50(5): 241-45 | ISSN: 1578-2735

26. Kurosawa Keiko, Terao Takeshi, Masayuki Kanehisa, Ippei Shiotsuki, Ishii Nobuyoshi, Ryuichi Takenaka, Sakamoto Teruo, Matsukawa Takehisa, Yokoyama Kazuhito, Shuntaro Ando, Atsushi Nishida, Matsuoka Yutaka. Naturally absorbed polyunsaturated fatty acids, lithium, and suicide-related behaviors: A case-controlled study. Journal of Affective Disorders. 2018;241:200–205.
27. Nikoline N. Knudsen, Jörg Schullehner, Birgitte Hansen, Lisbeth F. Jørgensen, Søren M. Kristiansen, Denitza D. Voutchkova, Thomas A. Gerds, Per K. Andersen, Kristine Bihrmann, Morten Grønbæk, Lars V. Kessing, Annette K. Ersbøll. Lithium in Drinking Water and Incidence of Suicide: A Nationwide Individual-Level Cohort Study with 22 Years of Follow-Up. Int. J. Environ. Res. Public Health. 2017;14:627. DOI: 10.3390/ijerph14060627.
28. Janusz K. Rybakowski. Lithium-the benefits of long-term treatment. Bipolar Disorders. 2020;00:1-2. DOI: 10.1111/bdi.13033.
29. Tarun Bastiampillai, Steven S. Sharfstein, Stephen Allison. Increasing the Use of Lithium and Clozapine in US Suicide Prevention.2017;74(4):423.
30. Katharine A Smith, Andrea Cipriani. Lithium and suicide in mood disorders: Updated meta-review of the scientific literatura. Bipolar Disorders. 2017;19:575–586. DOI: 10.1111/bdi.12543.
31. Robert M Post. The New News about Lithium: An Underutilized Treatment in the United States. Neuropsychopharmacology. 2018;43:1174-1179. DOI: 10.1038/npp.2017.238.