LITHIUM: OLD AND NEW OBSERVATIONS

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I. INTRODUCTION

The modern history of lithium started in 1949, when John Cade, an Australian psychiatrist, used it to treat people with mania and found rapid and dramatic improvements. Lithium became a registered medication in various countries: France in 1961, the United Kingdom in 1966, Germany in 1967, Italy and the USA in 1970.
Lithium is a soft, silvery-white alkali metal with atomic number 3 detected in trace amounts in animal tissues. Unlike sodium and potassium, it develops a relatively small distribution gradient across biological membranes. Although it is able to replace sodium to induce an action potential in nerve cells, it does not constitute an adequate substrate for the sodium pump, thus not being able to increase the membrane potential.

Nowadays, immediate-release and prolonged-release lithium formulations are available for human use.

Nevertheless, more than 60 years after its approval, lithium remains the first-line treatment for preventing manic and depressive episodes of bipolar disorder. Lithium has also proven useful in major depression, particularly for augmentation of antidepressants, and for aggressive behavior, and it has a specific antisuicide effect; its use for cluster headache is only indicated in individuals who do not respond to other therapies. This medication is additionally indicated for the Kleyne-Levine syndrome, for psychogenic polydipsia and as an augmentation strategy in treatment-resistant patients with schizophrenia. Immunomodulatory, antiviral and neuroprotective effects contribute to the therapeutic effects of lithium.

II. GENETICS

Not all patients treated with lithium salts have the same clinical response. About 20 – 30% of patients have a sustained improvement in the course of the disease, with a remarkable reduction or even absence of affective episodes (lithium responders); about 30% of patients are only partially responsive (partial responders) and more 40% have no clinical response at all to lithium [1]. Genetics can only explain a small part of this variability, and other mechanisms are involved [2]. Patients with a complete response to lithium therapy come from families with the same complete response and disease pattern. Genes that code for GSK-3β, BDNF and the serotonin transporter are robust candidates to be associated with lithium response in bipolar disorder. An independent prospective sample of patients treated with lithium for 2 years showed that those patients who were carriers of good-response genetic variants in the chromosome 21 locus had a significantly lower relapse rate than non-carriers patients in the same study [1].

III. PHARMACOKINETICS

Lithium is administered as oral tablets. It is well absorbed at the gastrointestinal level with an oral bioavailability of 80-100%. Lithium is not bound to plasma proteins and has a volume of distribution around 0.7 – 1.0 L/Kg; it is not metabolized by hepatic cytochromes and is eliminated as a free ion in the kidney. The plasma half-life is approximately 24 hours; the stationary stage is obtained between the fifth and eighth day. It is excreted in urine for 90%. The immediate-release formulations are rapidly absorbed and achieve peak serum concentrations (C-max) in 1-2 h after oral administration, while C-max values for prolonged-release are 4-5 h.

In order to have a therapeutic effect, lithium crosses the blood-brain barrier and the blood-cerebrospinal fluid barrier. The effective plasma concentrations are between 0.4 – 1.0 mEq/L. According to the recent racommendations issued by the ISBD/IGSLI, the standard lithium serum level should be 0.60 – 0.80 mmol/L, with the option to reduce it to 0.40 – 0.60 mmol/L in case of good response but poor tolerance, or to increase it to 0.80 – 1.00 mmol/L in case of insufficient response and good tolerance. Concentrations between 1.5 – 2.5 mEq/L can produce serious toxic phenomena when concentrations exceed 2.5 mEq/L and deadly when they exceed 3.5 mEq/L [3]
The most clinically relevant pharmacokinetic drug interactions occur when lithium is co-administered with drugs reducing renal elimination (thiazide and loop diuretics, nonsteroidal anti-infiammatory drugs, angiotensin-converting enzyme inhibitors) or that increase renal excretion (theophylline, caffeine, sodium bicarbonate, products containing sodium chloride).

IV. PHARMACODYNAMIC

It is now established that lithium affects multiple steps in cellular signaling.
In animal studies, it has been shown to increase serotonin transmission by multiple mechanisms, including increased synthesis of serotonin, increased tryptophan uptake and increased serotonin release.

Following acute administration, it increases glutamate release, blocks glutamate reuptake and stimulates NMDA receptors by competing with magnesium ions. After several days, these effects are reversed, and lithium reduces synaptic concentrations of glutamate by increasing and stabilizing its reuptake.

Lithium administration does not seem to reduce basal dopaminergic tone but inhibits increased dopaminergic activity, possibly via action on β-arrestin complexes [4].

One of the main biochemical mechanisms of lithium is related to inhibition of the glycogen synthase kinase-3β (GSK-3β) and the consequent effects on intracellular signaling, especially the phosphatidylinositol system. GSK-3β has been known to regulate gene expression, embryonic development, neuronal survival, synaptic plasticity, apoptosis, cellular structure and resilience, and circadian rhythms, all of which are implicated in the pathophysiology of mood disorders [5].

Lithium inhibits inositol monophosphatase-1 as well as protein kinase C (PKC) and also influences the adenyl cyclases, which convert ATP into cyclic adenosine monophosphate (cAMP). The key element of this system is the cAMP response element-binding protein (CREB), the regulator of gene expression. Additionally, lithium influences the brain-derived neurotrophic factor (BDNF), which is necessary for the survival and function of neurons. The enhancement by lithium of the BDNF system plays a role in its mood-stabilizing and probably also has neuroprotective activity. Long-term lithium treatment was found to increase intracellular and extracellular BDNF in cortical and hippocampal neurons. The upregulation of BDNF is possibly a downstream consequence of lithium's direct inhibition of the GSK3β activity. Lithium partially reverses telomere shortening in patients with bipolar disorder [4].

The mechanism underlying the protective effect on suicidal thoughts and behaviour is still unclear; several mechanisms seem to be involved, such as agonist properties on serotonergic receptors or increased glutamate release and activation of the gabaergic system [3].

Pharmacodynamic drug interactions are less frequent and may occur when combining lithium with selective serotonin reuptake inhibitors; first generation antipsychotics. In particular, some medications, such as SSRI, NSAIDs, ACE inhibitors, angiotensin-II receptor antagonists, thiazides, spironolactone, furosemide, metronidazole, tetracyclines, topiramate, may increase serum levels of lithium concentrations.

V. SIDE EFFECTS

The most common side effects of lithium include lithium-induced nephrogenic diabetes insipidus and lithium nephropathy. Renal side effects associated with lithium include polyuria, nephrogenic diabetes insipidus, proteinuria, distal renal tubular acidosis, and reduced glomerular filtration rate. Histologically, chronic lithium nephrotoxicity is characterized by interstitial nephritis with microcyst formation and occasional focal segmental glomerulosclerosis.

The most frequent lithium-induced thyroid adverse effects are goiter and hypothyroidism. The symptoms of hypothyroidism usually appear at the early stage of lithium treatment and are more frequent in women and persons with a family history of thyroid dysfunction.

Among other lithium side effects that can be troubling, the tremor occurring at the beginning of lithium therapy and weight gain can be mentioned. [3].

VI. LITHIUM DURING PREGNANCY

Managing Bipolar Disorder in pregnancy is highly problematic since there are risks associated with the use of mood stabilizers as well as in the absence of such treatments, and these risks have not yet been thoroughly examined or quantified. This causes treatment decisions based on risks that are only partially known. [6;7;8; 9; 10; 11; 12; 13; 14; 15; 16; 17;18; 19]

Lithium is an ion that freely crosses the placental barrier [20]. Congenital malformations, particularly cardiovascular, have been associated with lithium use during the first trimester of pregnancy. Data from a registry of children exposed to lithium during gestation showed a 400-fold increase in cardiac malformations, and in particular Ebstein's anomaly, in the exposed children compared with the general population [21; 22].

This anomaly is characterized by downward dislocation of the tricuspid valve, right ventricular dysfunction and tricuspid regurgitation [23] and has an incidence in the general population of 1:20000. Cohen et al. [24] analyzed published studies on lithium exposure during pregnancy and found that the incidence of cardiovascular malformations with lithium use in early pregnancy was 0.05-0.1%, 10 to 20 times higher than the rate of cardiovascular abnormalities in the general population, although the risk was much lower than once believed.

Diav-Citrin et al. [25] compared the rate of congenital abnormalities in lithium-exposed, disease-matched, and non-lithium-exposed pregnancies. The occurrence of cardiovascular abnormalities was higher in the lithium-exposed group, although this difference was not significant after excluding abnormalities that resolved spontaneously.

Patorno et al. [26] used data from the Medicaid registry in the United States to study 1,325,563 pregnancies, of which 663 were exposed to lithium and 1945 were exposed to lamotrigine. They found a dose-dependent association between lithium exposure and cardiac malformations, including Ebstein's anomaly. The adjusted hazard ratio for cardiac malformations was calculated as 1.65 compared with controls and 2.25 compared with lamotrigine-exposed. The risk of cardiac malformations was estimated to be in the range of one additional case per 100 live births. The same study found no association between lithium exposure and noncardiac malformations.

In contrast, in a recent meta-analysis [27] of 727 lithium-exposed pregnancies and 21,397 disease-matched controls, the risk of major malformations (including cardiac malformations) was increased in lithium-exposed pregnancies (OR 1.62, 95% CI 1.12- 2.33) compared with unexposed pregnancies in mothers with mood disorders, while there was no statistically significant increase in the risk of cardiac malformations. Although this evidence is not conclusive, it is recommended to discuss lithium continuation with women with bipolar disorder before and during pregnancy. One option might be to reduce lithium during the first trimester, but the risk of relapse must be weighed if this option is considered. If lithium is continued, a fetal cardiac ultrasound should be performed at 20 weeks of gestational age but could be recommended earlier, at 16 weeks [28].

The pathophysiology of the association between lithium and congenital malformations is not clearly known; it could be related to lithium's inhibition of glycogen synthase kinase-3β (GSK3β), as its expression is fundamental for the Wnt signaling pathway, which participates in cardiac and vascular development in the embryo [28; 29; 30; 31].

Maternal lithium clearance is not constant during pregnancy but in the second half it gradually increases from 30% to 50%. The clearance undergoes, however, a sudden drop after delivery, returning to pre-pregnancy values [32]. Increased lithium dosages during pregnancy to compensate for the increased clearance may induce toxicity. In general, it is recommended to discontinue lithium

during the last days of pregnancy to reduce the risk of lithium toxicity for the mother due to accumulation and to reinstate it at a low dose after delivery to avoid the risk of manic and/or depressive relapse [28].

Knowledge about the course of Bipolar Disorder during pregnancy remains limited, and the risk of relapse is not well quantified. In fact, while the risk of relapse is well-defined in the postpartum period, during pregnancy, it remains uncertain.

A recent review by Salim [33] examined this issue, suggesting that a substantial number of women with BD experience relapses during pregnancy, most commonly depressive episodes. Included studies found a higher proportion of recurrence among participants who discontinued treatment with mood stabilizers [34; 35; 36; 7].

Regarding the postpartum period, large retrospective cohort studies suggest that the risk of at least one episode of BD (of any polarity) is estimated to be between 40% and 55% of women with BD who have a history of recurrent episodes within the first six months after delivery [37]

A recent meta-analysis of mostly retrospective data indicates that about 37% of women with BD are affected in the postpartum period [38]. The risk of mania and/or psychosis is particularly high immediately after childbirth in women with BD [39]; in fact, these women are 37 times more likely to go under psychiatric hospitalization than at any other time in their lives [40]. In particular, women with bipolar I disorder (BD I) and schizoaffective disorder-bipolar type (SA-BD) are particularly vulnerable.

Guidelines do not agree on the best treatment strategy during pregnancy. Hence, NICE guidelines (NICE 2014) [41] recommend considering discontinuation of lithium in the first trimester and switching to another antipsychotic. In the case of lithium therapy, the woman should be informed of the teratogenic risks.

On the other hand, Australian and New Zealand guidelines [42] suggest that lithium is the most effective drug in preventing relapse and antipsychotics can be used as an alternative.

A. What to do in case of pregnancy?

Based on literature data, here is a list of practical directions to follow in patients on lithium therapy during pregnancy. [43].

1. Maintain lithium concentration at minimum protective levels for the individual.
2. In case of lithium exposure in the first trimester of pregnancy, possible cardiac malformations can be diagnosed by prenatal screening with a high-resolution ultrasound examination (level II) and echocardiography at 16-18 weeks of gestation. [44; 45]
3. Monitor lithium concentrations periodically: the NICE and NVVP guidelines recommend at least monthly monitoring during the first 7-8 months of pregnancy; during the last phase, from 34 weeks until delivery, when marked changes in glomerular filtration rate occur that may alter lithium clearance, weekly monitoring is recommended. [38]
4. Lithium renal excretion increases during the different phases of pregnancy, so dose increases will be necessary to keep lithium blood levels constant [46].
5. Some authors suggest dividing the daily dose of lithium into multiple administrations to avoid high exposure peaks in the unborn child [47].
6. Avoid therapeutic interventions that may increase the risk of lithium toxicity (e.g., ACE inhibitors, diuretics, NSAIDs, low-sodium diet), or, if necessary, an adjustment in lithium doses is required [35].
7. Reduce lithium dose in case of complications such as preeclampsia or polyhydramnios that may predispose to lithium toxicity [35].
8. Discontinue lithium administration 24-48 hours before planned cesarean delivery or induced delivery, or at the beginning of labor in the case of spontaneous delivery. [35]
9. In case of spontaneous delivery, check maternal lithium concentration when the patient arrives at the hospital [35].
10. Maintain adequate hydration with oral and/or intravenous fluids during the labor and delivery process and monitor maternal lithium concentration in case of clinical signs of toxicity [35].
11. Lithium therapy should be reintroduced after delivery as soon as the patient is medically stable. The pre-conception dose should be used as the glomerular filtration rate returns to previous levels [35].
12. Lithium is secreted in breast milk, so breastfeeding should be avoided [8].

VII.CONCLUSIONS

Lithium represents the gold standard of long-term treatment of bipolar disorder, but patient management requires skills and experience [4], and its use is safe within specialized clinics [48].

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