**Lithium: old and new observations**

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1. **INTRODUCTION**

The modern history of lithium started in 1949, when an Australian psychiatrist, John Cade, used it to cure patients with mania and found a significant improvement [1]. 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 is the first-line treatment for preventing manic and depressive episodes of bipolar disorder”* [2]. Lithium is recommended in: *“major depression, augmentation of antidepressants, aggressive behavior, and suicide prevention”*; 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, psychogenic polydipsia and as an augmentation and combination strategy in treatment, resistant patients with schizophrenia [1]. Immunomodulatory, antiviral and neuroprotective effects contribute to the therapeutic effects of lithium [3].

1. **GENETICS**

The patients treated with lithium salts behave differently. About 20 – 30% of patients have a sustained improvement in the course of the disease [4], with partial or complete improvement (lithium responders); the remaining patients are “partial responders” (30%) or “no responder (40%) [4]. Genetics can only explain a small part of this variability, and other mechanisms are involved [5]. Patients with a complete response to lithium therapy come from families with the same complete response and disease pattern. Candidate genes to be associated with lithium response [4] encoding for GSK-3β, BDNF and the serotonin transporter. Patients carrying good response genetic variants in the chromosome 21 locus have a significantly lower relapse rate than non-carrier patients [4].

1. **Pharmacokinetics**

Lithium is in the form of oral tablets. It is well absorbed at the gastrointestinal level with an oral bioavailability of 80-100% [1]. Lithium is not bound to plasma proteins; the ditribuition volume of lithium is around 0.7 – 1.0 L/Kg; hepatic cytochromes do not metabolized this volume and it is eliminated as a free ion in the kidney [1]. 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”* [1].

Lithium crosses the blood-brain barrier and the blood-cerebrospinal fluid barrier [1]. The effective plasma concentrations are between 0.4 – 1.0 mEq/L. The 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 (ISBD/IGSLI), [1] . 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 [1].

Drugs reducing renal excretion of lithium or increase it represent the most clinically relevant pharmacokinetic drug interactions with lithium [1]

1. **Pharmacodynamic**

It is now established that lithium affects multiple steps in cellular signaling.

The increase in serotonergic transmission (synthesis of serotonin, tryptophan uptake, serotonin release) was evidenced in animal studies [2].

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 [2].

Lithium administration does not seem to reduce basal dopaminergic tone but inhibits increased dopaminergic activity, possibly via action on β-arrestin complexes [2].

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”* [6].

Lithium inhibits inositol monophosphatase-1, protein kinase C (PKC) and influences the adenyl cyclases, which convert ATP into cyclic adenosine monophosphate (cAMP). Gene expression is regulated by cAMP response element-binding protein (CREB), primary elemet of this system [6].

Additionally, lithium influences the brain-derived neurotrophic factor (BDNF), which is necessary for the survival and function of neurons; in this way lithium plays a role in its mood-stabilizing and probably also has neuroprotective activity [6]. Long-term lithium treatment was found to increase intracellular and extracellular BDNF in cortical and hippocampal neurons. Direct inhibition of the GSK3β activity could upregulate BDNF [2].

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 [1].

Pharmacodynamic drug interactions may occur when dispensing lithium with selective serotonin reuptake inhibitors, first generation antipsychotics; they are less frequent [1]. Some medications may increase serum levels of lithium concentrations.

1. **SIDE EFFECTS**

Nephrogenic diabetes insipidus and lithium nephropathy are the most common side effects of lithium [1]. Renal side effects associated with lithium include polyuria, nephrogenic diabetes insipidus, proteinuria, distal renal tubular acidosis, and reduced glomerular filtration rate [7]. Histologically, chronic lithium nephrotoxicity is characterized by interstitial nephritis with microcyst formation and occasional focal segmental glomerulosclerosis [7].

Goiter and hypothyroidism are the most frequent thyroid adverse effects [8]. The symptoms of hypothyroidism are more frequent in women and persons with a family history of thyroid dysfunction and usually appear at the early stage of lithium treatment [8].

The tremor, that can occurr at the beginning of lithium therapy, and weight gain can be mentioned among other lithium side effects [8].

1. **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. [9; 10; 11; 12; 13; 14 ; 15; 16; 17; 18; 19; 20; 21; 22].

Lithium is an ion that freely crosses the placental barrier [23]. 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 [24], in the exposed children compared to the non-exposed [25].

Ebstein's anomaly has an incidence, in the general population, of 1:20000; downward dislocation of the tricuspid valve [24], right ventricular dysfunction and tricuspid regurgitation [26] are its characteristics. Cohen et al. [27] 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 [13].

Diav-Citrin et al. [28] compared pregnancies lithium-exposed and non-lithium-exposed and he observed the possible appearance of congenital abnormalities in two groups. The incidence of cardiovascular abnormalities was higher in the lithium-exposed group [28], but excluding abnormalities that resolved spontaneously, this difference was not statistically significant.

Patorno et al. extracted data from the Medicaid registry in the United States to study 1,325,563 pregnancies (663 were exposed to lithium and 1945 were exposed to lamotrigine) [29]. The association between lithium exposure and cardiac malformations, including Ebstein's anomaly, was dose-dependent [29]. The adjusted hazard ratio for cardiac malformations was calculated as 1.65 compared with controls and 2.25 compared with lamotrigine-exposed [29]. The risk of cardiac malformations was evaluated to be in the range of one additional case per 100 live births [29]. This study *“did not find any association between lithium exposure and noncardiac malformations"* [29].

In contrast, in a meta-analysis of 727 lithium-exposed pregnancies and 21,397 disease-matched controls, *“the risk of major malformations (including cardiac malformations) was higher in lithium-exposed pregnancies (OR 1.62, 95% CI 1.12- 2.33) compared with unexposed pregnancies in mothers with a diagnosis of mood disorders”,* while there was no statistically significant increase in the risk of cardiac malformations [30]. Although *“this evidence is not conclusive”,* it is recommended to discuss lithium continuation with women with bipolar disorder before and during pregnancy. For example, it might be useful to reduce lithium during the first trimester, but in this case the risk of relapse must be 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”* [31].

The pathophysiology of congenital malformations in fetusis exposed to lithium is not clearly known: lithium's inhibition of glycogen synthase kinase-3β (GSK3β)? [34]; its expression is fundamental for the Wnt signaling pathway [33], which participates in cardiac and vascular development in the embryo [31; 32].

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 [35]. 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 [31].

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 examined this issue, suggesting that a substantial number of women with BD experience relapses during pregnancy, most commonly depressive episodes [36]. Included studies found a higher proportion of recurrence among participants who discontinued treatment with mood stabilizers [36] [37; 38; 39; 10].

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% [40] of women with BD who have a history of recurrent episodes within the first six months after delivery [40].

A recent meta-analysis indicates that about *“37% of women with BD are affected in the postpartum period”* [41]. The risk of mania and/or psychosis is particularly high immediately after childbirth in women with BD [42]; in fact, these women are 37 times more likely to go under psychiatric hospitalization than at any other time in their lives [43]. In particular, women with *“bipolar I disorder (BD I) and schizoaffective disorder-bipolar type (SA-BD) are particularly vulnerable”* [43].

Guidelines do not agree on the best treatment strategy during pregnancy. Hence, NICE guidelines (NICE 2014) [44] 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 [45] suggest that lithium is the most indicated drug to prevent relapses and antipsychotics could be 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. [46].

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”.* [47] [48]

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 modifications in glomerular filtration rate occur that may change lithium clearance, weekly monitoring is recommended. [41]

4. Lithium renal excretion increases during the different phases of pregnancy, so dose increases will be necessary to keep lithium blood levels constant [49].

5. Some authors suggest dividing the daily dose of lithium into multiple administrations to avoid high exposure peaks in the unborn child [50].

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 [38].

7. Reduce lithium dose in case of *“complications such as preeclampsia or polyhydramnios”* that may predispose to lithium toxicity [38].

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 [38].

9. In case of *“spontaneous delivery, check maternal lithium concentration when the patient arrives at the hospital”* [38].

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”* [38].

11. Lithium therapy should be reintroduced after delivery when the patient is medically stable. The pre-conception dose should be used as the glomerular filtration rate returns to previous levels [38].

12. Lithium is secreted in breast milk, so breastfeeding should be avoided [11].

1. **Conclusions**

Lithium represents the gold standard of long-term treatment of bipolar disorder, but patient management requires skills and experience [2], and its use is safe within specialized clinics [51].

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