Low-Dose Lithium

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Abstract

Lithium in nearly toxic doses is the gold standard for the treatment of bipolar disorder. In the early 20th century, small amounts of lithium were commonly added to carbonated water (e.g. soda or seltzer water) and promoted as a relief for alcoholic hangovers. Recent research shows that lithium is neuroprotective and may protect against the loss of neurons induced by ethanol. In addition, trace amounts of lithium found naturally in tap water have been shown to be associated with a lower rate of suicide. This article begins with a brief review of lithium, its medical use and toxicity, followed by a discussion of low-dose lithium, and ends with research on how to reduce toxic side effects with natural therapies.

Lithium

Discovered by Arfvedson in 1817, lithium is the lightest of all metals, with a density only about half that of water. Trace amounts of lithium are present in the oceans and in all organisms. The element serves no apparent vital biological function, since animal and plants survive in good health without it. Non-vital functions have not been ruled out. Lithium is found in small units in nearly all igneous rocks and in many mineral springs. Lithium is not a dietary mineral for plants but it does stimulate plant growth.

Medical Uses

Lithium (Eskalith, Lithobid) is used to treat and prevent episodes of mania (frenzied, abnormally excited mood) in people with bipolar disorder (manic-depressive disorder; a disease that causes episodes of depression, episodes of mania, and other abnormal moods). Lithium continues to be the gold standard for the treatment of bipolar disorder.

Mechanism of Action

Lithium has been shown to elevate brain levels of tryptophan, 5-HT (serotonin), and 5-HIAA (a serotonin metabolite). Lithium also reduces catecholamine activity in the brain (associated with brain activation and mania), by enhancing reuptake and reducing release. (Price, Charney et al. 1989)

Amyotrophic Lateral Sclerosis (ALS)

A recent study found that daily doses of lithium, leading to plasma levels ranging from 0.4 to 0.8 mEq/liter, delay disease progression in human patients affected by ALS. (Fornai, Longone et al. 2008)

Conventional Dosage

Desirable serum lithium concentrations are 0.6 to 1.2 mEq/L, which can usually be achieved with 900-1200 mg/day, although it may be increased to 2700 mg/day. Dosage will vary from one individual to another, but generally the following dosages will maintain this concentration: 2 tabs Lithobid (600 mg) in the morning and at night.

- Eskalith contains 300 mg of lithium carbonate.
- Eskalith CR contains 450 mg in Controlled-Release tablets
- Lithobid (lithium carbonate) is an extended-release formulation containing 300 mg of lithium carbonate.

Toxicity

Therapeutically useful amounts of lithium (1.0 to 1.2 mmol/L) are only slightly lower than toxic amounts (>1.5 mmol/L), so the blood levels of lithium must be carefully monitored during treatment to avoid toxicity.

Large doses of lithium (up to 10 mg/L in serum) are given to patients with bipolar disorder. At 10 mg/L of blood, a person is mildly lithium poisoned. At 15 mg/L they experience confusion and speech impairment, and at 20 mg/L Li there is a risk of death. (Aral and Vecchio-Sadus 2008)

Because it is minimally protein bound, lithium is freely filtered at a rate that is dependent upon the glomerular filtration rate (GFR). Consequently, dosing must be adjusted based on renal function. Individuals with chronic renal insufficiency must be closely monitored if placed on lithium therapy.

Side Effects

Common side effects of lithium treatment include muscle tremors, twitching, ataxia, and hypothyroidism. Long-term use is linked to hyperparathyroidism, hypercalcemia (bone loss), hypertension, damage of tubuli in the kidney, nephrogenic diabetes insipidus (polyuria and polydipsia) and/or glomerular damage – even to the point of uremia, seizures and weight gain.

Thyroid

Lithium inhibits thyroid hormone release from the thyroid gland, and can be used as an adjunct therapy in the management of severe hyperthyroidism (thyrotoxicosis). (Lazarus 2009) (Ng, Tiu et al. 2006)

Goiter is a common clinical side effect of lithium in up to 40%, and hypothyroidism in about 20%. Lithium increases thyroid autoimmunity if present before therapy. (Lazarus 2009)

Neuroprotection

The main mechanism underlying lithium's neuroprotective effects is thought to be inhibition of glycogen synthase kinase-3 (GSK-3). (Camins, Verdaguer et al. 2009)

Evidence from pharmacological and gene manipulation studies support the notion that glycogen synthase kinase-3 inhibition and induction of brain-derived neurotrophic factor-mediated signaling are lithium's main mechanisms of action, leading to enhanced cell survival pathways and alteration of a wide variety of downstream effectors. By inhibiting N-methyl-D-aspartate receptor-mediated calcium influx, lithium also contributes to calcium homeostasis and suppresses calcium-dependent activation of pro-apoptotic signaling pathways. In addition, lithium decreases inositol 1,4,5-trisphosphate by inhibiting phosphoinositol phosphatases, a process recently identified as a novel mechanism for inducing autophagy. (Chiu and Chuang 2010)

Lithium was found for the first time to stimulate the biogenesis of mitochondria in the central nervous system and, uniquely in the spinal cord, it induces neuronogenesis and neuronal differentiation. In particular, the effects induced by lithium can be summarized as follows: (Fornai, Longone et al. 2008)

(i) The removal of altered mitochondria and protein aggre- gates;
(ii) The biogenesis of well-structured mitochondria;
(iii) The suppression of glial proliferation;
(iv) The differentiation of newly formed neurons in the spinal cord towards a specific phenotype.

Alcohol

Ethanol induces a loss of neurons in the central nervous system. Recent in vivo and in vitro studies indicate that lithium is able to ameliorate ethanol-induced neuroapoptosis. (Luo 2010)

A double-blind placebo-controlled study of 122 patients meeting DSM-III criteria for alcohol dependence and hospitalized for alcoholism rehabilitation found that lithium carbonate promotes abstinence from alcohol and delays the time to first drink. Patients treated with lithium were much less likely to be re-hospitalized for alcoholism rehabilitation during the 18-month follow-up. (Sartori 1986)

Low-Dose Lithium

In contrast to conventional medical dosage (900-2700 mg/day), low-dose lithium therapy is a small fraction, typically 5-15 mg/day.

Lithium orotate and citrate

Lithium orotate (orotic acid) is sometimes marketed as a "safe" natural alternative with fewer side effects than conventional lithium (carbonate).

Lithium citrate was the medicinal ingredient of a refreshment beverage, 7 Up. Charles Leiper Grigg, who launched his St. Louis-based company The Howdy Corporation in 1920, invented a formula for a lemon-lime soft drink in 1929. The product, originally named "Bib-Label Lithiated Lemon-Lime Soda", was launched two weeks before the Wall Street Crash of 1929. It contained lithium citrate and was one of a number of patent medicine products popular in the late-19th and early-20th centuries. The beverage was marketed specifically as a hangover cure and was marketed as such with an early marketing slogan of "It takes the ouch out of grouch". Its name was soon changed to 7 Up. (El-Mallakh and Roberts 2007)

Suicide

In 2009, Japanese researchers at Oita University examined lithium levels (0.7–59 gm/l) in tap water in the 18 municipalities of Oita prefecture in Japan in relation to the suicide standardized mortality ratio (SMR) in each municipality. They found that lithium levels were significantly and negatively associated with SMR averages for 2002-2006. (Ohgami, Terao et al. 2009)

It has been proposed that increasing lithium levels of drinking water could potentially reduce the risk of suicide, and justify administering lithium to tap water. (Terao, Goto et al. 2009)

Thyroid

Lithium in drinking water has been shown to increase TSH. Women (N=202) were recruited in four Andean villages in Northern Argentina. Lithium exposure was assessed based on concentrations in spot urine samples. Thyroid function was evaluated by plasma free thyroxine (T4) and pituitary gland thyroid-stimulating hormone (TSH). The median urine lithium concentration was 3,910 mug/L (5th/95th percentiles 270/10,400 microg/L). Median plasma concentrations (5th/95th percentiles) of T4 and TSH were 17 pmol/L (13/21 pmol/L) and 1.9 mIU/L, (0.68/4.9 mIU/L), respectively. Urine lithium was inversely associated with T4 (beta for a 1000-mug/L increase -0.19, 95% CI -0.31 to -0.068; p=0.002) and positively associated with TSH (beta=0.096, 95% CI 0.033 to 0.16; p=0.003). Both associations persisted after adjustment (T4: beta=-0.17, 95% CI -0.32 to -0.015; p=0.032; TSH: beta=0.089, 95% CI 0.024 to 0.15; p=0.007). Urine selenium was positively

associated with T4 (adjusted T4 for a 1-mug/L increase: beta=0.041, 95% CI 0.012 to 0.071; p=0.006). (Broberg, Concha et al. 2011)

Protection Against Lithium Toxicity

Several mechanisms have been proposed to explain the action and toxicity of lithium. The following may help reduce the side effects:

Linoleic acid (in safflower oil)

Inositol

Folate

Aspirin

Linoleic acid

An article published in *Prostaglandins and Medicine* stated that lithium inhibits the synthesis of prostaglandin (PG) El by blocking the mobilization of dihomogammalinolenic acid (DGLA). The toxicity due to lithium might be related to reduced PGEl formation.

In five patients who developed toxic effects on low doses of lithium, linoleic acid in the form of safflower oil was given in an attempt to raise levels of the linoleic acid metabolite, DGLA. In all five patients the safflower oil was effective in remitting the symptoms of neurotoxicity. Safflower oil was also effective in a patient with familial tremor. (Lieb 1980)

In a pilot study, six patients were given evening primrose oil (Efamol, 500 mg, 2 capsules four times a day for four days). One patient showed aggravation of tremor after discontinuation of propranolol, reduction of tremor intensity after having been given Efamol for four days, aggravation after discontinuation of Efamol, no improvement on repeated Efamol treatment for four days, and no further aggravation of tremor when switched (without her knowledge) to placebo capsules. None of the five other patients showed any change in tremor intensity, subjectively or objectively, during administration of Efamol. (Schou 1980)

The Inositol-Depletion Hypothesis

Over 20 years ago Berridge et al proposed the inositol-depletion hypothesis in an attempt to explain the therapeutic mechanism of lithium. (Deranieh and Greenberg 2009) (Harwood 2005) (Berridge, Downes et al. 1989; Berridge and Irvine 1989)

Lithium reduces brain inositol levels by inhibiting the enzyme inositol monophosphatase. (Hallcher and Sherman 1980) (Kofman and Belmaker 1993)

An older study found that high-dose peripheral inositol raises brain inositol levels and reverses the behavioral effects of inositol depletion by lithium. (Agam, Shapiro et al. 1994)

A recent study found that lithium induces synapse formation via inositol depletion and subsequent down-regulation of the phosphoinositide signaling cascade. (Kim and Thayer 2009)

Folate

A recent study showed that folate might protect against human congenital heart and neural tube defects that have been linked to elevated plasma homocysteine (HCy), which results from folate deficiency, and the mood-stabilizing drug lithium (Li). (Han, Serrano et al. 2009)

In 107 patients on long-term lithium, those with lower plasma folate concentration had a higher affective morbidity than those with higher folate, both at the time and during the previous two years. (Coppen and Abou-Saleh 1982)

A double-blind trial was carried out to investigate the effect on affective morbidity of a daily supplement of 200 micrograms folic acid or a matched placebo in a group of 75 patients on lithium therapy. During the trial the patients with the highest plasma folate concentrations showed a significant reduction in their affective morbidity. Patients who had their plasma folate increased to 13 ng/ml or above had a 40% reduction in their affective morbidity. (Coppen, Chaudhry et al. 1986)

Aspirin

Aspirin down-regulates markers of the brain arachidonic acid metabolic cascade, including phospholipase A2 and cyclooxygenase (COX) expression. (Stolk, Souverein et al. 2010)

A recent study found that low-dose aspirin produced a statistically significant duration-independent reduction in the relative risk of clinical deterioration in subjects on lithium, whereas other NSAIDs and glucocorticoids did not. (Stolk, Souverein et al. 2010)

Nitric Oxide

A recent study found that nitric oxide metabolism (i.e. the L-arginine / NO / cGMP pathway) is involved in the antidepressant-like effects of acute lithium administration in the mouse forced swimming test. The authors recommended the concurrent administration of NOS inhibitors and lithium as an appropriate strategy for treatment of depression. (Ghasemi, Sadeghipour et al. 2008)

Conclusion

Low doses of lithium may be of benefit for those with depression and a history of alcoholism. The recommended are significantly lower than those known to cause toxic side effects. In addition, linoleic acid (safflower oil), inositol, folate and aspirin may help reduce side effects, although the research is limited.

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