Side Effects and Toxicity of Lithium

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Although lithium remains the most specific treatment for bipolar affective disorder, it should be cautiously prescribed and used only when clinically indicated. The main indications for lithium are the manic phase of bipolar affective disorder and prophylaxis of both manic and depressive episodes. Lowering serum lithium levels will markedly reduce the incidence of side effects, and patients should be maintained at the lowest possible serum level. The serum level may be as low as 0.4 mEq/L and as high as 1.5 mEq/L, depending on the clinical response of the patient and the presence of side effects. The most controversial areas are the possibility of renal toxicity and the concomitant use of lithium with neuroleptics, especially haloperidol.

In addition to its well-studied use in affective disorders, lithium has been used in at least 30 other psychiatric and nonpsychiatric conditions.[1,2] Even within the therapeutic serum lithium range, as many as two thirds of patients suffer from persistent, unwanted side effects.[3] In addition, the concomitant use of other drugs, the presence of other disease states, and special physiological states, such as pregnancy, must also be considered as potentially inducing lithium side effects.[4]

The most serious side effects are mainly associated with lithium poisoning. Patients on lithium therapy should be evaluated prior to treatment and be closely monitored and followed during treatment, thus preventing the development of lithium poisoning and serious adverse reactions. Current recommendations include monitoring kidney functioning, at least with serial creatinines and general chemistry, and monitoring thyroid functions with a thyroid-stimulating hormone (TSH) level every six months.

Patients taking other medication, especially diuretics and neuroleptics, should be followed particularly closely to prevent the possibility of lithium toxicity. Patient education is also imperative, and a well-informed patient will make the task of the physician much easier.

Effects of Lithium on the Major Body Systems

Central Nervous System

The effects of lithium on the central nervous system range from commonly observed mild ef-

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fects to life-threatening, irreversible brain damage, which occurs in rare cases of severe toxicity.

In therapeutic serum ranges, lithium produces electroencephalographic slowing. In a study of normal subjects taking lithium, lethargy, lassitude, anxiety, tension, and feelings of loss of clearheadedness with an inability to concentrate were noted. Lithium was felt to exert a central effect by slowing the rate of cognitive processing.[5] Rapid eye movement (REM) sleep is also suppressed, with lengthening of REM latency and an increase of slow wave sleep.[6] Grand mal seizures may occur, temporal lobe epilepsy may be exacerbated, short-term memory may be impaired, and states of confusion may appear.[7,8] Hyperthermia and difficulties in achieving and maintaining erections have been described.[9] Classical parkinsonian syndrome symptoms may appear, which may be made worse by antiparkinsonian drugs.[10,11] It is not clear whether lithium alone produces these or whether some individuals are more vulnerable to the neurotoxicity of antipsychotic drugs.

Above the therapeutic range, possible toxic effects of lithium include dysarthria, cogwheel rigidity, convulsions, and coma. Schizophrenic patients and patients with pre-existing neurological disorders are possibly more likely to develop these problems, although Schou[2] has questioned whether schizophrenic patients are more likely to develop neurological symptoms.

Neuromuscular Effects

The two major neuromuscular effects are hand tremor and muscular weakness.

Men complain significantly more often than women of hand tremor—54 percent vs 33 percent.[12] This tremor is similar to a benign essential tremor, namely, a fine rapid tremor (but no so fine as in hyperthyroidism) most readily observed when body parts are held in positions of sustained posture. The tremor is improved with propranolol, but not with anticholinergics, which may even make the tremor worse.[13] In fact, a patient taking tricyclic antidepressants and neuroleptics may develop a more severe tremor.

General mild muscle weakness is often a transient effect at the beginning of treatment. At the extreme, a syndrome similar to myasthenia gravis has been reported to be associated with lithium therapy. Muscular hyperirritability, twitching, and fasciculation may also occur as a direct effect of lithium. There may be an elevation of creatinine phosphokinase (CPK), which has theoretically been related to lithium-induced hypothroidism.

Renal Effects of Lithium

Recently a great deal of concern has been expressed about the possibility of kidney damage from long-term lithium therapy. The possibility has been raised of a situation analogous to that of tardive dyskinesia associated with psychotropic drugs.[14,15]

Rafaelsen et al[16] suggested that functional or morphological evidence of renal damage occurs in 6 to 15 percent of patients on long-term lithium therapy. Some patients on lithium treatment show interstitial fibrosis and nephron atrophy on kidney biopsy[17]; but recently, Coppen et al[18] concluded that there was little evidence of a serious renal functional impairment attributable to lithium therapy. Also, Jenner[19] feels that no clear serious lithium damage has been proven. According to Schou and Verstergaard[20] there is significantly more nephropathy in patients given lithium than in completely healthy normal controls, but nonspecific changes of the same kind, and occurring to almost the same extent, can be found in patients with longstanding affective illness not yet treated with lithium.

More common but less serious is the appearance of polyuria and polydipsia. This occurs in more than one half the patients starting lithium treatment, and approximately one quarter continue to exhibit these symptoms one to two years after initiation of treatment. Some patients develop a syndrome similar to diabetes insipidus that may be resistant to vasopressin (Pitressin).[21] Cases of nephrotic syndrome have been reported.[22]

Renal functioning should be monitored before and during lithium therapy. Current recommendations include a serum creatinine in the evaluation every three to six months, and the results should be closely observed in relation to increased values within the normal range as well as raised absolute

abnormal values. Urine osmolality following a 12-hour overnight dehydration and a 24-hour urine volume and protein should be monitored every six months. The creatinine clearance test should be done if either the serum creatinine or the urine volume are abnormal. In a hospital setting, the creatinine clearance test would be the preferred baseline test. Serum creatinine alone might not be sensitive enough to detect slight changes in glomerular filtration rate.[23] DePaulo et al[23] recommend at least that a Cockroft-type creatinine clearance (CC) be calculated as follows:

$$CC = \frac{(140 - \text{age})\ (\text{weight [kg]})\ (.85\ [\text{female only}])}{72 \times \text{serum creatinine}}$$

It is conceivable that lithium may be nephrotoxic in rare cases, but more data are needed to reach a conclusion. The data are inconclusive about the possibility of serious renal damage occurring to the kidney of patients *within* therapeutic range levels of lithium. Ayd[24] has recommended lower total daily lithium dosages, lower serum levels, and possibly lithium holidays in some patients as a way of dealing with the possible nephrotoxicity of lithium.

In a recent article that followed up 237 patients on long-term treatment, Vestergaard et al[25] found neither the patients who continued nor the patients who had discontinued lithium had shown any deterioration of glomerular filtration rate as assessed through determination of 24-hour creatinine clearance and the serum creatinine concentration. Lithium-treated patients had the same mean values as control manic-depressive patients not yet given lithium. Impairment of renal water resorption, as revealed by increased 24-hour urine volume and decreased urine osmolality after 1-desamino-8-D-arginine vasopressin (DDAVP) had progressed in patients who continued lithium treatment. This was found to be related to the duration of treatment and the serum lithium levels; however, in patients who had discontinued lithium, these values tended to revert back to normal.

Hematological Effects

Lithium produces a relative leucocytosis in most patients that may be persistent or periodic. This is due to neutrophilia and is accompanied by lymphocytosis. This reaction does not appear to have any adverse effects and reverses when lithium is discontinued.[26] Megaloblastic anemia has also been reported.[27]

Cardiac Effects

Lithium treatment has been associated with a wide range of cardiac complications. These include T wave changes, myocarditis, and ventricular arrhythmias.[28,29] These effects may be related to a partial replacement of potassium by lithium in the myocardium. Cardiac sinus node dysfunction proved to be lithium dependent by Holter monitoring was reported by Roose et al.[28] Hagman et al[29] also found that lithium treatment can result in node dysfunction.

Gastrointestinal Tract

Gastrointestinal tract side effects are common at the onset of treatment and appear to be related to the rapidity of rise of serum lithium levels.[3] Ten percent of patients suffer from persistent gastrointestinal tract side effects, and mild diarrhea may occur in 20 percent of patients during initial therapy. Other side effects include gastric irritation, epigastric bloating or pressure, abdominal pain, nausea, emesis, and anorexia.

Contact stomatitis has also been reported with lithium carbonate.[30]

Thyroid Gland

Lithium has an inhibiting effect on the thyroid gland through the following mechanisms[31]: inhibition of iodine uptake into the thyroid, inhibition of iodination of tyrosine, inhibition of release of triiodothronine (T_3) and thyroxine (T_4) from the thyroid, inhibition of peripheral degradation of thyroid hormone, and inhibition of adenyl cyclase,

causing thyroid-stimulating hormone (TSH) stimulation of the thyroid.

Five percent of patients taking lithium develop hypothyroidism and 3 percent develop benign diffuse nontoxic goiter. Because of its antithyroid actions, lithium has been used in the treatment of thyrotoxicosis. On rare occasion lithium has been reported to produce thyrotoxicosis.

Patients with elevated thyroid antibodies prior to lithium use are more vulnerable to the antithyroid action. Regular monitoring of serum TSH is the most reliable method of detecting any problems with thyroid functioning and should be done at six-month intervals.

Parathyroid Gland

Lithium may cause biochemical hyperparathyroidism with elevated serum calcium, lowered serum phosphate concentrations, and increased urinary calcium excretion.[32]

Metabolic Effects

Weight gain greater than 10 kg is common and occurs in 10 to 20 percent of patients. Lithium does have an insulin-like effect on gluconeogenesis, and it also produces changes in lipid metabolism. Lithium patients will, of course, compound their weight gain if increased thirst is satisfied with beverages high in calories. In addition, edema of feet and legs may occur while taking lithium.

Dermatological Effects

Skin problems are allegedly uncommon and include a transient maculopapular rash, alopecia, pruritic dermatitis, ulceration, acne, exacerbation of psoriasis, and folliculitis.[7] These lesions, however, are probably underreported by patients who do not link cause and effect.

Drug Interactions

Jefferson et al[33] has recently reviewed these in detail by class of drug. These can be classified under interference with absorption, distribution, and disposition.

Altered Absorption Lithium has been shown to lower serum chlorpromazine levels.[34] Tetracycline may cause diarrhea, which reduces sodium absorption, thereby raising serum lithium levels.[35]

Distribution Lithium is distributed in the body water with only a slow penetration into the intracellular compartment. Concurrent administration of methyldopa with lithium causes toxicity associated with a decrease in plasma concentrations of the drug, whereas cessation of methyldopa alleviates toxicity while plasma concentrations rise. This suggests a movement of lithium from the extracellular fluid to the intracellular fluid under the influence of methyldopa.[36-38]

Disposition Lithium clearance may be decreased by about 25 percent with thiazide diuretics.[4] A compensatory increase of sodium resorption in the proximal tubules induced by the thiazide increases lithium resorption, thereby decreasing its clearance. Decreased dietary sodium intake might also raise lithium to toxic levels by a similar mechanism. In the opposite direction, patients ingesting high levels of dietary sodium may demonstrate little clinical progress on normal dosages of lithium.

Xanthines may also affect lithium pharmacokinetics by increasing its excretion. Thus, a marked increase of coffee, tea, or cola ingestion (as often occurs in the inpatient setting) could decrease serum lithium levels, whereas a decrease of these fluids could increase serum lithium levels.

Indomethacin, ibuprofen, and phenylbutazone may also reduce the renal clearance of lithium, possibly because of reduced synthesis of prostaglandin-E_2 (PE_2) in the distal tubule.[39] In addition to these drugs, whether any or all of the other prostaglandin synthetase inhibitors, including mefenamic acid, naproxen, sulindac, and zomepirac, affect serum lithium levels remains to be determined.

Tetracyclines may also cause toxic raising of serum lithium levels by their action on the kidney and by affecting sodium absorption.[40]

Toxicity in Combination with Haloperidol and Other Neuroleptics

In 1974 Cohen and Cohen[41] reported an alarming encephalopathic condition in four patients in the same hospital receiving lithium and haloperidol. In 1976 London and Waring[42] reported seven patients with this same medicinal combination who developed severe persistent extrapyramidal side effects that did not respond to antiparkinsonian agents.

A review of the literature by Strayhorn and Nash[43] found nine cases of neurotoxicity associated with concomitant neuroleptic and lithium use. Toxic reactions with lithium and concomitant use of other neuroleptics have also been recently reported by others.[44,45]

Ayd[46] is of the opinion that moderate doses of lithium and haloperidol can be safely coadministered. He felt that in each of the neurotoxicity cases described, the patients' symptoms could be attributed primarily to lithium. When treating highly agitated, severely disturbed patients, combining high doses of both haloperidol and lithium is not advised, and in any event, the delayed onset of action of lithium makes it of little value for acute behavioral control.[47]

The whole question of lithium-neuroleptic interaction has again been laid open following a recent article by Spring,[48] describing a case with neurological symptoms similar to those described by Cohen and Cohen. He distinguishes two types of lithium-neuroleptic interactions. The first is associated with neuroleptics having strong dopamine-blocking actions such as haloperidol. The second type is the enhanced lithium neurotoxicity associated with phenothiazines, especially thioridazine, which may cause elevated intracellular lithium.[49]

Tupin and Schuller[50] summarize the issue: "After good clinical control is achieved with a neuroleptic, lithium can then be added in low doses and gradually increased for long-term prophylaxis. During this time, the neuroleptic can be decreased and discontinued as appropriate serum lithium levels are achieved."

Charney[51] reported somnabulistic episodes associated with electroencephalogram changes in patients on lithium-neuroleptic combinations.

Finally, it has also been found that lithium syrup forms a precipitate when mixed with at least two oral concentrates of antipsychotic drugs, chlorpromazine (Thorazine) and trifluoperazine (Stelazine). Lithium syrup should never be mixed into "cocktails" with phenothiazine concentrates.

Toxicity with Electroconvulsive Therapy

Although the data are inconclusive and the mechanisms unknown, lithium administered concurrently with electroconvulsive therapy does seem to increase the likelihood of confusion and delirium.[52]

Pregnancy

Lithium may be teratogenic during pregnancy, especially the first trimester, and most notably causes Ebstein's anomaly.[53,54]

Lithium crosses the placenta easily and may cause hypotonia in the neonate. It is also excreted in breast milk.[54] Mizrahi et al described a case of diabetes insipidus in a neonate that persisted for four months, although lithium was undetectable in the baby's serum after day 4.[55]

Rane and Bjarke[54] reported a case of dextrocardia and coarctation of the aorta occurring in a child of a lithium-treated mother.

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