Lithium-Drug Interactions

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The goal of maintenance therapy for bipolar disorder is to prevent relapses, reduce subthreshold symptoms, decrease suicide risk, reduce cycling frequency and mood instability, and improve overall functioning. Lithium was approved by the FDA in 1970 for the treatment of mania in bipolar disorder. This agent may act as a mood stabilizer by altering sodium transport in nerve and muscle cells, which results in enhanced intraneuronal metabolism of catecholamines. Although several antiepileptics and antipsychotics have been approved by the FDA for the treatment of bipolar disorder, lithium remains a first-line option.

Lithium is associated with clinically relevant drug interactions, which are summarized in the Table. Understanding the propensity of certain drugs to increase or decrease lithium concentrations is vitally important because this mood stabilizer is recommended as initial therapy in patients with bipolar disorder. Recognition of potential drug interactions can minimize the risk of adverse effects and toxicity while maximizing therapeutic efficacy.

**RISK OF LITHIUM TOXICITY**
Because the therapeutic range for lithium is very narrow, careful serum concentration monitoring and dosage adjustments are required in order to maintain efficacy and prevent toxicity. Patients who take lithium should be instructed to discontinue the drug and contact the prescriber if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur. Severe lithium intoxication may result in life-threatening cardiac arrhythmias and death. As an alkali metal and monovalent cation, lithium is not biotransformed or highly protein-bound but is excreted unchanged by the kidneys. Therefore, any drug that has the potential to reduce renal function may lead to accumulation of lithium. Drugs with nephrotoxic potential should generally be avoided in patients who are receiving lithium.

Drug-drug interactions may contribute to altered lithium serum concentrations and decreased efficacy or increased toxicity. In particular, drugs that affect sodium or water balance may result in interactions with lithium. **LITHIUM DRUG INTERACTIONS**

**Diuretics.** Lithium is eliminated primarily through glomerular filtration. Nearly 75% of lithium ions are reabsorbed in the renal tubules by passive diffusion; thus, medications with pharmacological action in the renal tubules can potentially interact with lithium. In 3 separate studies, thiazide diuretics, when added to lithium therapy, increased lithium serum concentrations by 26.5%, 25%, and 23.3%, respectively. In order to manage this drug interaction, the recommended empiric lithium dosage reduction is 25% to 40% when thiazide diuretics are added to lithium therapy. Close monitoring of lithium serum concentrations and careful observation for signs or symptoms of lithium intoxication are essential during the first week of treatment. Clinical evidence that loop diuretics decrease lithium concentrations is limited. A case study of 6 patients who received furosemide or ethacrynic acid reported decreases of 11% and 2%, respectively, in lithium clearance. These data, when combined with those from Saffer and Coppen, suggest that loop diuretics are unlikely to significantly interact with lithium unless a confounding medical condition such as fluid imbalance or hemodynamic instability is present. The influence of osmotic diuretics on lithium excretion in both animals and humans has been well documented. Osmotic diuretics create ionic gradients in the renal tubules that promote the excretion of water along with lithium and sodium. Lithium clearance increases by about 36% when osmotic diuretics are used in combination with lithium. Concomitant therapy with osmotic diuretics and lithium causes a significant drug interaction, but the probability that these agents would be
administered together is remote. Differences in the effects of various potassium-sparing diuretics on lithium concentrations have been reported. While amiloride and triamterene do not affect lithium levels,\textsuperscript{14,15} spironolactone increases lithium concentrations by 16\% when given concomitantly.\textsuperscript{10} Although this interaction may not produce a significant rise in serum lithium concentrations, spironolactone should be considered as having the potential to interact with lithium.

Some data suggest that the methylxanthine derivatives, theophylline, aminophylline, and caffeine, can potentially decrease lithium serum concentrations.\textsuperscript{10,16-18} Initial reports with single-dose aminophylline and lithium clearance demonstrated a 58\% increase in renal excretion of lithium.\textsuperscript{10} Perry and colleagues\textsuperscript{16} reported that lithium clearance was increased by an average of 30\% when theophylline was given to 10 healthy volunteers who had been receiving lithium for 9 days. In an open-label, prospective evaluation of psychiatric patients by Mester and associates,\textsuperscript{17} caffeine withdrawal was found to increase serum lithium concentrations by an average of 24\%. The potential for this drug interaction seems to be greatest when methylxanthines are discontinued after concomitant therapy with lithium.

A few studies have shown that interactions between lithium and carbonic anhydrase inhibitors, such as acetazolamide, reduce lithium serum concentrations through inhibition of proximal and distal reabsorption. Thomsen and Schou\textsuperscript{10} evaluated acetazolamide and lithium therapy and reported a 27\% increase in lithium clearance. This evidence is consistent with a rat model that demonstrated a 36\% increase in lithium elimination following acetazolamide administration.\textsuperscript{14} Further evaluations need to be performed to substantiate this drug interaction.

**Angiotensin-converting enzyme (ACE) inhibitors.** These drugs have been well-documented to increase serum lithium concentrations, even leading to lithium toxicity in some cases, although the precise mechanism is not understood. In a case-control study, Finley and coworkers\textsuperscript{19} found on average a 36\% increase in serum lithium concentrations; 4 patients in the study presumably had lithium toxicity. The drug interaction can be delayed for up to 2 months after an ACE inhibitor is initiated; lithium serum levels should be monitored closely during this time. The angiotensin II receptor antagonists can also raise lithium levels.

**NSAIDs.** Substantial evidence supports an interaction between lithium and NSAIDs. However, important differences exist among the various agents in this class. Indomethacin potentiated lithium toxicity in 2 case reports\textsuperscript{20,21} and increased lithium serum concentrations an average of 20\% to 59\% in 2 case-control studies.\textsuperscript{22,23} Although serum lithium concentrations increased by 40\% with indomethacin coadministration, no effect was seen on lithium levels when aspirin was coadministered.\textsuperscript{23} Other case studies have shown that aspirin and sulindac have no effect on serum lithium concentrations.\textsuperscript{24,25} Studies have also demonstrated that the COX-2 selective drugs, such as rofecoxib and celecoxib, have the potential to increase lithium levels. Prospective evaluations need to be conducted regarding the effect of other NSAIDs, such as mafenamic acid, piroxicam, and ketorolac, on lithium concentrations; but case reports have shown the potential for these agents to increase serum lithium levels.\textsuperscript{26-30}

References: REFERENCES:

4. Lithium [package insert].


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