

Loop diuretics and angiotensin-converting enzyme inhibitors increased risk for hospitalization for lithium toxicity

Juurlink DN, Mamdani MM, Kopp A, et al. Drug-induced lithium toxicity in the elderly: a population-based study. *J Am Geriatr Soc.* 2004;52:794-8.

QUESTION

In older persons, is use of diuretics, angiotensin-converting enzyme (ACE) inhibitors, or nonsteroidal antiinflammatory drugs (NSAIDs) associated with hospital admission for lithium toxicity?

METHODS

Design: Population-based, nested, case-control study with analysis of multiple linked health care databases over 10 years.

Setting: Ontario, Canada.

Patients: 10 615 patients \geq 66 years of age (mean age 72 y, 62% women) who were receiving uninterrupted lithium treatment and resided in Ontario, Canada.

Risk factors: Use of a diuretic (alone or in combination with another agent), ACE inhibitor, or prescription NSAID (including cyclooxygenase-2 inhibitors). Thiazide-type and loop diuretics were examined separately.

Outcome: Hospital admission with diagnosis of lithium toxicity within 28 days of exposure.

MAIN RESULTS

413 patients (3.9%) had \geq 1 hospital admission for lithium toxicity. After adjustment for potential confounders, patients treated with a loop diuretic or ACE inhibitor in the preceding 28 days had modest increased risk for hospital admission for lithium toxicity (Table); these increased risks were particularly high among patients newly treated with loop diuretics or ACE inhibitors in the preceding 28 days (Table). Patients treated with thiazide diuretics, NSAIDs, or topical corticosteroids did not have increased risk

for hospitalization for lithium toxicity, even during the first month of treatment.

CONCLUSION

In older persons, the use of loop diuretics or angiotensin-converting enzyme inhibitors increased risk for hospital admission for lithium toxicity, especially during the initial month of treatment.

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Association between medication use and hospital admission for lithium toxicity in older persons*

Medication exposure	Adjusted relative risk (95% CI)
Any use of loop diuretics	1.7 (1.1 to 2.7)
Any use of ACE inhibitors	1.6 (1.1 to 2.3)
New use of loop diuretics (\leq 28 d)	5.5 (1.9 to 16.1)
New use of ACE inhibitors (\leq 28 d)	7.6 (2.6 to 22.0)

*ACE = angiotensin-converting enzyme. Relative risks adjusted for other potential interacting medications, previous admission for lithium toxicity, renal disease, and number of different prescription drugs in the preceding year.

COMMENTARY

Since the 1950s, lithium has been the drug of choice for treating bipolar affective disorder. Its optimal steady-state concentration for maintenance therapy is generally considered to be 0.6 to 1.2 mEq/L, but the therapeutic index is rather narrow because toxicity occurs at levels $>$ 1.5 mEq/L and could even be present at lower levels. Lithium is excreted by glomerular filtration, and close monitoring of serum levels is mandatory in patients with altered renal function or who are receiving ACE inhibitors or NSAIDs (1). Older patients with decreased glomerular filtration rate (GFR) are at risk for renal insufficiency after diuretic-induced volume contraction, and it is likely that patients treated with long-term lithium are at higher risk for toxicity because of tubular damage and impaired sodium reabsorption (2, 3). This could also partly explain why the risk for lithium intoxication is so high in patients newly treated with ACE inhibitors.

The observation of Juurlink and colleagues, that patients newly treated with loop diuretics also have increased risk much higher than that associated with recent thiazide treatment, deserves other explanations. 60% of filtered lithium is reabsorbed in the proximal tubule, in a way similar to that of sodium, and 20% more is reabsorbed between the loop of Henle and the collecting duct. As for sodium, furosemide increases lithium clearance by blocking loop reabsorption, and thiazides

do the same by blocking distal reabsorption. However, 3 pharmacologic differences could explain the distinctive effects of these drugs on the risk for lithium intoxication. First, a decrease in loop reabsorption increases the amount of lithium arriving in the distal tubule and induces a compensatory distal reabsorption that limits net excretion changes. Second, furosemide is a potent stimulator of the renin-angiotensin system, which could increase proximal lithium reabsorption. Third, the shorter effect of furosemide is followed by large "sodium-avid" periods, during which lithium balance could become positive enough to result in lithium intoxication.

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