Loop diuretics and angiotensin converting enzyme inhibitors increased risk of hospital admission for lithium toxicity


Clinical impact ratings GP/FP/Primary care ★★★★★☆ IM/Ambulatory care ★★★★★☆ Emergency Medicine ★★★★★☆ Neurology ★★★★★☆ Geriatrics ★★★★★☆

Q In older persons, is use of diuretics, angiotensin converting enzyme (ACE) inhibitors, or non-steroidal anti-inflammatory drugs (NSAIDs) associated with hospital admission for lithium toxicity?

METHODS

Design: population based, nested, case control study with analysis of multiple linked healthcare databases over 10 years.

Setting: Ontario, Canada.

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

Assessment of risk factors: use of 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 ≥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 of 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 an increased risk of hospital admission 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 the risk of 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

<table>
<thead>
<tr>
<th>Medication exposure</th>
<th>Adjusted relative risk (95% CI)</th>
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<tbody>
<tr>
<td>Any use of loop diuretics</td>
<td>1.7 (1.1 to 2.7)</td>
</tr>
<tr>
<td>Any use of angiotensin converting enzyme (ACE) inhibitors</td>
<td>1.6 (1.1 to 2.3)</td>
</tr>
<tr>
<td>New use of loop diuretics (&lt;28 d)</td>
<td>5.5 (1.9 to 16.1)</td>
</tr>
<tr>
<td>New use of ACE inhibitors (&lt;28 d)</td>
<td>7.6 (2.6 to 22.0)</td>
</tr>
</tbody>
</table>

*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 0.6–1.2 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 concentrations. Lithium is excreted by glomerular filtration, and close monitoring of serum concentrations is mandatory in patients with altered renal function or who are receiving ACE inhibitors or NSAIDs. Older patients with decreased glomerular filtration rate (GFR) are at risk of renal insufficiency after diuretic induced volume contraction, and it is likely that patients treated with long term lithium are at higher risk of toxicity because of tubular damage and impaired sodium reabsorption. This could also partly explain why the risk of lithium intoxication is so high in patients newly treated with ACE inhibitors.

The observation of Juurlink et al, 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 pharmacological differences could explain the distinctive effects of these drugs on the risk of lithium intoxication. Firstly, 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. Secondly, furosemide is a potent stimulator of the renin-angiotensin system, which could increase proximal lithium reabsorption. Thirdly, 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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