Concomitant loop diuretics and ACE inhibitors increase risk of lithium toxicity in elderly people


Q In elderly people, is lithium toxicity associated with concomitant use of diuretics, angiotensin converting enzyme inhibitors, or nonsteroidal anti-inflammatory drugs?

METHODS

**Design:** Nested case control study.

**Follow up period:** 10 years (January 1992 to December 2001).

**Setting:** Analysis of linked healthcare databases, Ontario, Canada.

**People:** 10,615 people, aged ≥66 years (62% women), treated continuously with lithium. Four controls, matched for age, sex, and lithium use were selected (randomly where more than four were identified).

**Risk factors:** Diuretics, including thiazide-type (such as chlorothalidone) and loop diuretics (such as furosemide), angiotensin converting enzyme (ACE) inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors, taken concomitantly with lithium.

**Outcomes:** Hospital admission for lithium toxicity (ICD-9 criteria).

**MAIN RESULTS**

Over 10 years, 413 people (4%) receiving continuous treatment with lithium were admitted into hospital at least once for lithium toxicity. Of these, 15% required critical care, 3% dialysis, and 5% died before discharge. Existing use of loop diuretics and ACE inhibitors was associated with a modestly increased risk of lithium toxicity. Initiating loop diuretics or ACE inhibitors significantly increased the risk of lithium toxicity: within one month of starting treatment. Loop diuretics and ACE inhibitors taken concomitantly with lithium significantly increase the risk of lithium toxicity within one month of beginning treatment.

### Table Relative risks of hospitalisation for lithium toxicity and association with other medications

<table>
<thead>
<tr>
<th>Treatment begun</th>
<th>All users (RR, 95% CI)</th>
<th>New users (RR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 28 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>1.3 (0.7 to 2.9)</td>
<td>1.3 (0.3 to 4.7)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>1.7 (1.1 to 2.7)</td>
<td>5.5 (1.9 to 16.1)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>1.6 (1.1 to 2.3)</td>
<td>7.6 (2.6 to 22.0)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.1 (0.8 to 1.6)</td>
<td>0.6 (0.2 to 2.1)</td>
</tr>
</tbody>
</table>

*RRs adjusted for other potential interacting medications.*

CONCLUSIONS

Loop diuretics and ACE inhibitors taken concomitantly with lithium significantly increase the risk of lithium toxicity within one month of beginning treatment.

### Commentary

A glance at the latest British National Formulary1 shows that the potential for diuretics and ACE inhibitors to cause lithium toxicity is well known. This excellent paper not only provides robust evidence for it, but also points to the need to refine advice to clinicians. It is probably true to say that most geriatricians and old age psychiatrists believe that angiotensin converting enzyme (ACE) inhibitors, diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) should be prescribed with extra care to elderly patients taking lithium. What this paper shows is that ACE inhibitors newly prescribed (that is, within the last month) to those already taking lithium carry the greatest risk of toxicity (RR = 7.6).

A more important new finding is that, where diuretics are concerned, it is loop not thiazide diuretics that carry the greater relative risk (RR = 5.5) for older people—the very opposite of what is stated in the BNF (page 652), “loop diuretics safer than thiazides”, which may be true for younger patients but not any more for older ones.

Taken at face value, this paper might indicate that thiazide diuretics and NSAIDs are relatively safe to prescribe to patients taking lithium; not that the authors actually suggest it. However, the clinician would be wise to reserve judgement and consider the possibility of a type II error or other more subtle reasons for caution. For instance, a thiazide diuretic prescribed in a long, hot summer to an elderly person whose arthritis makes it difficult to get to the tap (faucet) for water can have the same result of toxicity as a loop diuretic in winter.

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