Effects of lithium on kidney, thyroid and parathyroid function

A retrospective cohort study of UK laboratory data found that lithium use for a median of 3 years was associated with an increased risk of kidney disease, hypothyroidism and hyperparathyroidism.

Overview:
- A retrospective cohort study found that using lithium for a median of 3 years was associated with an increased risk of kidney, thyroid and parathyroid disease.
- NICE recommends that lithium is the most effective long-term pharmacological treatment to prevent relapse in people with bipolar disorder.
- Biochemical monitoring may be appropriate in people treated with lithium, and abnormal test results should prompt review of the risks and benefits of continuing treatment.

Background: Lithium is commonly used to prevent episodes of mania or depression in people with bipolar disorder. Long-term treatment with lithium can affect the kidneys, thyroid and parathyroid gland (McKnight et al. 2012). However, the clinical significance of these effects and the risk factors for developing kidney disease or endocrine disorders are not clear.

Current advice: The NICE guideline on bipolar disorder recommends that lithium is the most effective long-term pharmacological treatment to prevent relapse in people with bipolar disorder.

People with bipolar disorder who are starting lithium should undergo tests for urea and electrolytes including calcium, estimated glomerular filtration rate (eGFR), thyroid function and a full blood count. In addition, their weight or BMI should be measured. After starting lithium treatment, tests should be arranged every 6 months for urea and electrolytes including calcium, eGFR and thyroid function.

The NICE pathway on bipolar disorder brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: Shine et al. (2015) retrospectively analysed UK laboratory data from a single hospital trust to assess the incidence of kidney, thyroid and parathyroid dysfunction in people receiving lithium.
Routine collected data for 1985 to 2014 were extracted from the laboratory information system of a hospital trust in Oxford. The study cohort comprised all people aged 18 years or older who had at least 2 measurements of lithium, serum creatinine, thyrotropin, calcium or glycated haemoglobin (HbA1c). The control group was made up of all other people in the laboratory system of the same sex and age but with no lithium measurements recorded.

Glomerular filtration rate was estimated from age, sex and serum creatinine concentration. Decline in renal function was defined as stage 3 chronic kidney disease (CKD); that is, an eGFR of less than 60 ml/min/1.73m². Hypothyroidism was defined as thyrotropin activity of more than 5.5 mU/l, and hyperthyroidism as thyrotropin activity of less than 0.2 mU/l. More than 2.6 mmol/l was used as the threshold for raised total serum calcium concentration or serum calcium concentration adjusted for albumin levels, which are signs of hyperparathyroidism.

The cohort for analysis comprised 2795 people who had more than 1 measurement of serum lithium concentration and 689,228 controls. People taking lithium had been receiving the drug for a median of 3 years (max 28 years) and had a median serum concentration 0.6 mmol/l.

After adjustment for age, sex and evidence of diabetes, lithium treatment was significantly associated with decline in renal function (hazard ratio [HR]=1.93, 95% confidence interval [CI] 1.76 to 2.12, p<0.0001), hypothyroidism (HR=2.31, 95% CI 2.05 to 2.60, p<0.0001), and raised total serum calcium concentration (HR=1.43, 95% CI 1.21 to 1.69, p<0.0001). However, lithium was not significantly associated with hyperthyroidism or raised adjusted calcium concentration.

The main risk factors for renal and thyroid disease were female gender and age, with the risk highest in women under 60 years of age (HR for renal disease=2.05, 95% CI 1.86 to 2.25, p<0.0001 and HR for hypothyroidism=2.37, 95% CI 2.10 to 2.69, p<0.0001).

In subgroup analyses, serum lithium concentration greater than 0.6 mmol/l was associated with increased risk of all adverse outcomes. The risks of renal and thyroid disease were not raised in people who had been receiving lithium for more than 3 years, indicating that the adverse effects of lithium were likely to occur early in treatment.

The strengths of this study are the large number of participants and the length of follow-up. However, no information was available on the primary psychiatric diagnosis of people taking lithium, or on the dose or formulation of lithium used.

**Commentary by Carol Paton, Chief Pharmacist, Oxleas NHS Foundation Trust and Thomas Barnes, Professor of Clinical Psychiatry, Imperial College, London:**

"NICE considers lithium to be the most effective prophylactic treatment for people with bipolar disorder (NICE 2014). Also well-established is the narrow therapeutic range of lithium and its potentially harmful effects on both the kidneys and thyroid. However, the quality of lithium monitoring often falls short of recognised standards and targets (Collins et al. 2010) and this prompted a patient safety alert from the National Patient Safety Agency (NPSA 2009). There is some evidence that UK practice is improving (Paton et al. 2013) but gaps between practice and recommended standards remain.

"Using routinely collected laboratory data, Shine et al. (2015) examined the effect of lithium treatment on renal function. They concluded that, compared with people who are not prescribed lithium, people who are prescribed lithium have a greater decline in renal function over time and a larger proportion have stage 3 CKD. They also found that young women and those with a plasma lithium level greater than 0.6 mmol/l were at greater risk, as were all people in the early stages of treatment. Some of these associations are relatively new and have implications for clinical practice.

"The authors acknowledge that variables potentially associated with the outcome of interest, such as psychiatric diagnosis and the clinical reason for each sample being tested, were not available. An eGFR threshold of less than 60 ml/min/1.73m² alone was used to indicate stage 3 CKD in this study. Further diagnostic investigations are warranted to accurately diagnose stage 3 CKD (Kripalani et al. 2013)."
so the prevalence of CKD may have been overestimated.

“Further, the median plasma lithium level of 0.6 mmol/l was used as a threshold for the analysis, and those people with higher levels had a greater decline in renal function. However, it is not clear if there is a critical toxicity threshold level above this median, even within the accepted therapeutic range (up to 1.0 mmol/l in some cases), or whether past discrete episodes of high plasma lithium levels are relevant. There is some evidence to suggest that the threshold for harm may be 1.0 mmol/l (Kirkham et al. 2014).

“Although only a very small proportion of people treated with lithium develop end-stage renal disease, CKD is strongly associated with increased morbidity and mortality from cardiovascular disease. Biochemical monitoring is essential in all people treated with lithium, as recommended by NICE guidance. Abnormal test results should prompt expert review of the risks and benefits of continuing treatment.”

Study sponsorship: This study was not funded.

About this article: This article appeared in the November 2015 issue of the Eyes on Evidence awareness service.

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