Adverse drug reaction

Asthma precipitated by cessation of lithium treatment

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Summary

We report symptomatic asthma, associated with objective and highly significant increases in both airway responsiveness and airflow limitation, presenting *de novo* in a male patient 6 weeks after suddenly discontinuing lithium carbonate therapy.

Keywords: adverse drug reaction; asthma; lithium

Increased mortality from asthma in both those who use or have recently used major tranquilizers has recently been described.^{1,2} Conversely, improvement in asthma control has been reported during the treatment of schizo-affective disorders with lithium carbonate.³ We have recently observed symptomatic asthma presenting *de novo* in a male patient 6 weeks after suddenly discontinuing lithium carbonate therapy, and 3 months after he was recruited into an epidemiological survey of asthma prevalence in the general population.

Case report

A 37-year-old man, a lifelong non-smoker, had no respiratory symptoms, had never been diagnosed as having asthma, and had never taken anti-asthma therapy. He suffered from a bipolar schizo-affective disorder and had received oral lithium carbonate 1400 mg with sulpiride 600 mg daily for 14 years. The serum lithium was well within the recommended therapeutic range. Airway responsiveness was quantified during the survey by a PD₂₀ of 291 µg (the cumulative provoking dose of inhaled methacholine responsible for a 20% decrement in FEV₁).⁴ PD₂₀ values of less than 200 µg are generally associated with other evidence of active asthma, whereas values greater than 1000 µg are almost never associated with active disease. Values of 200–1000 µg represent a 'grey zone' where some subjects are symptomatic and some are not. Allergen skin prick tests were negative but serum total IgE was mildly elevated at 130 kU/l (normal <100).

Six weeks later he was noted to have an asymptomatic bradycardia (resting pulse rate of 44 beats/min) and lithium therapy was discontinued on the advice of a cardiologist, thyroid function proving to be normal. After a further 6 weeks he complained of nocturnal cough and exertional wheeze. Percentage predicted FEV₁ had fallen from 112 to 66% and airway responsiveness had increased markedly (PD₂₀ from 291 to 9 µg of methacholine). There was no evidence of intercurrent respiratory infection. The diagnostic use of a further lithium challenge was considered inappropriate in view of the previous bradycardia, and he was commenced on inhaled budesonide and terbutaline. This resulted in a rapid symptomatic and physiological improvement (figure). Within 4 weeks the FEV₁ had improved to 3.74 litres (100% predicted) and the PD₂₀ had increased to 214 µg (a 24-fold increase). Several months later the patient's mental state deteriorated and he discontinued his inhaled therapy with a subsequent increase in airway responsiveness and asthma symptoms.

Discussion

The development of asthma following cessation of lithium therapy has not, to our knowledge, been described before, nor has it been reported to the UK Committee on Safety of Medicines (personal communication). The relationship is biologically plausible, however, and the onset of asthmatic symptoms in our

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Figure

patient within 6 weeks of discontinuing lithium medication was associated with objective and highly significant increases in both airway responsiveness and airflow limitation. It was fortunate that baseline measurements had, by chance, been obtained only 3 months earlier at the time of our survey. The baseline level of airway responsiveness had been in the 'grey zone' where some subjects have mild symptoms but others do not, and so it is likely that our patient was rather more susceptible to developing asthma than the average subject without respiratory symptoms.

Improvement in asthma control during the course of lithium therapy has been recorded, and a double-blind trial of short-term lithium therapy in patients with asthma has shown an improvement in airway responsiveness.³⁻⁵ Furthermore, *in vitro* studies have shown that lithium partially inhibits the contractile response of airway smooth muscle, possibly by an effect on the inositol phospholipid-derived second messenger system.⁶ There is also evidence that lithium may influence intracellular concentrations of potassium, calcium and sodium, and there are conflicting data relating dietary sodium to airway responsiveness.⁷⁻⁸ There are consequently a number of mechanisms which might explain the phenomenon we have observed.

Bradyarrhythmias are well recognised to complicate lithium therapy even at therapeutic levels, with reduction in membrane depolarisation rate and attenuated electrical impulse propagation as the likely primary cause. Clinically significant sinus node dysfunction is uncommon, however, and in one study of a pacemaker population lithium treatment was noted with a prevalence of only 0.46%.⁹ The adverse effect on asthma, a common disorder

Adverse effects of lithium therapy

- neurological: drowsiness, lethargy, headache, memory impairment, fine tremor
- cardiovascular: conduction defects, T-wave changes
- renal: thirst, polyuria, nephrogenic diabetes insipidus
- gastrointestinal: nausea, vomiting, diarrhoea
- endocrine: hypothyroidism, hypoparathyroidism, hyperglycaemia
- miscellaneous: leucocytosis, skin rash, weight gain

Learning points

- lithium is a psychotropic drug which significantly improves airway responsiveness and asthma
- there is, nevertheless, a documented increase in respiratory mortality in patients using other psychotropic and antidepressant agents
- careful monitoring of asthma control is advisable when discontinuing lithium in patients with asthma
- altered sinus node function is a well established but uncommon adverse effect of lithium therapy
- altered cellular sodium transport may be the mechanism for both cardiac effects and changes in airway smooth muscle tone

in the population at large, from lithium withdrawal may consequently prove to be a more important complication of lithium therapy in epidemiological terms than the well-recognised cardiac complications. Careful monitoring of asthma control is advisable when discontinuing lithium carbonate.

- 1 Joseph KS, Blais L, Ernst P, Suissa S. Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquilisers. *BMJ* 1996;**312**:79-83.
- 2 Allen GM, Hickie I, Gandevia SC, McKenzie DK. Impaired voluntary drive to breathe: a possible link between depression and unexplained ventilatory failure in asthmatic patients. *Thorax* 1994;**49**:881-4.
- 3 Nasr SJ, Atkins RW. Coincidental improvement in asthma during lithium therapy. *Am J Psychiatry* 1977;**134**:1042-3.
- 4 Beach JR, Young CL, Avery AJ, *et al.* Measurement of airway responsiveness to methacholine: relative importance of the precision of drug delivery and the method of assessing response. *Thorax* 1993;**48**:239-43.
- 5 Knox AJ, Higgins BG, Hall IP, Tattersfield AE. Effect of oral lithium on bronchial reactivity in asthma. *Clin Sci* 1992;**82**: 407-12.

- 6 Sampson SR, Weiss Rotem C. Relaxant effects of lithium on guinea pig tracheal smooth muscle *in vitro*. *Br J Pharmacol* 1982;**75**:287-91.
- 7 Britton J, Pavord I, Richards K, *et al.* Dietary sodium intake and the risk of airway hyperreactivity in a random adult population. *Thorax* 1994;**49**:875-80.
- 8 Devereux G, Beach JR, Bromly C, *et al.* Effect of dietary sodium on airway responsiveness and its importance in the epidemiology of asthma: an evaluation in three areas of northern England. *Thorax* 1995;**50**:941-7.
- 9 Rosenqvist M, Bergfeldt L, Aili H, Mathe AA. Sinus node dysfunction during long term lithium treatment. *Br Heart J* 1993;**70**:371-5.