

Drug interactions with lithium: long known but still overlooked. An emblematic case.

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Lithium was introduced as an antimanic drug almost 70 years ago. Its use in the prophylaxis of manic and depressive episodes was subsequently reported. Lithium is still considered the most effective long-term therapy for bipolar disorder and is also effective in unipolar depression. However, concerns have frequently been raised about its safety, given its narrow therapeutic window. Indeed, lithium intoxications may be fatal.

We report an emblematic case of how well known drug interactions still put lithium patients at risk of severe consequences.

A 56-years-old Sardinian woman had been treated with lithium and antipsychotics since the age of 39 for bipolar schizoaffective disorder with onset at 25. She had fully responded and had been maintained within the therapeutic range (0.60-0.80 mmol/l) for the last 17 years. Her treatment was monitored at our lithium clinic according to our schedule, that provides a 6-to-8-week interval between checks. Each check comprises a general visit, a psychiatric evaluation, and 12-hour lithium serum concentration measurement. Routine laboratory, thyroid function tests, and a cardiology visit with electrocardiogram are requested on an annual basis. Over the last two years, the patient had taken lithium carbonate 600 mg/daily and olanzapine 5 mg/daily. Her last lithium serum concentration (November 2014) was 0.68 mmol/l. In December 2014, she was prescribed for the first time an antihypertensive medication (nebivolol 5 mg/daily). In March 2015, she came to our unit for her routine check. She complained polyuria and tremors, and asthenia that had worsened over the last two weeks. She reported that 3 weeks earlier her cardiologist had prescribed her a combination of ramipril 2.5 mg and hydrochlorothiazide 12.5 mg daily, as her hypertension had not been controlled with the beta-antagonist alone. The availability of our in-house laboratory allowed the immediate check of lithium serum concentration. As a 2.78 mmol/l value was found, the patient was promptly hospitalized. Lithium was withdrawn, the patient was rehydrated and recovered in a few days. Subsequently, her treating psychiatrist opted for substituting lithium with valproic acid.

We reported an adverse drug reaction to the Sardinian Regional Center of pharmacovigilance. The reaction was considered severe, as it had resulted in hospitalization. The Adverse Drug Reaction Probability Scale (Naranjo Algorithm) was consistent with a probable interaction between lithium and the antihypertensive medications.

This case is emblematic of how interactions that have been known for a long time can be still overlooked. The effects of both thiazides and ACE inhibitors on lithium clearance have been reported repeatedly (MacFie, 1975; Meyer et al. 2005), and are also clearly included in the patient information leaflet. Fortunately, our clinical practice of limiting intervals between checks at the lithium clinic, associated with a good adherence of this specific patient to our schedule, allowed a relatively early detection of the interaction and prevented the severe consequences that result from chronic lithium intoxication.

Given our 35-year experience in the lithium clinic, we are aware of the need for constant reminders to patients, family members and treating physicians in order to prevent out of range lithium levels. However, this case witnesses that even the most trivial events put lithium patients at risk of serious consequences. To confirm our suspicion, we have also conducted an exploratory survey of our register, and report details regarding 206 cases of unwanted lithium serum concentrations out of 8784 12-hour measurements made over the past four years.

Macfie (1975). *Br Med J.* 1(5956), 516.

Meyer et al. (2005). *Int Clin Psychopharmacol.* 20, 115-8.