

Lithium-induced bradycardia: A rare but serious adverse effect

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Mr. C, age 30, with schizoaffective disorder, bipolar type, *Cannabis* abuse, and nicotine dependence, has been enrolled in a Program of Assertive Community Treatment (PACT) for approximately 5 years. He presents to the PACT clinic for follow-up with his psychiatrist. Mr. C reports dizziness, lightheadedness, blurred vision, and nausea worsening over the last few days, and he appears drowsy and hypoactive. He does not report any chest pain, abdominal pain, swelling, cold extremities, shortness of breath, vomiting, diarrhea, or blood loss. Mr. C admits he has eaten only once daily for several weeks because of delusional ideation that he is responsible for others suffering from anorexia nervosa.

His medical history includes gastroesophageal reflux disease. Mr. C's medication regimen for the past year included total daily oral doses of benzotropine, 2 mg, divalproex extended-release, 1,000 mg, fluphenazine, 15 mg, and gabapentin, 300 mg. He also receives IM fluphenazine decanoate, 50 mg every 2 weeks; lithium, 600 mg/d, was added to his regimen 5 months ago. Vital signs include temperature 97°F, weight 162 lb, height 69 inches, blood pressure 105/64 mm Hg, heart rate (HR) 46 beats per minute (bpm), and respirations 18 breaths per minute.

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Because of Mr. C's complaints, appearance, and low HR, the psychiatrist calls emergency medical services (EMS). Although the paramedics recommend emergency transport to the hospital, Mr. C refuses. The psychiatrist instructs Mr. C to stop taking lithium because of suspected lithium-induced bradycardia and a concern that he may be more susceptible to lithium toxicity with prolonged anorexia nervosa. When nursing staff evaluate Mr. C the next day, his vitals are HR 60 bpm, respirations 20 breaths per minute, and blood pressure 124/81 mm Hg; his dizziness, blurred vision, lightheadedness, and nausea are resolved.


Laboratory tests reveal a low lithium level of 0.3 mEq/L (reference range, 0.6 to 1.2 mEq/L), a low valproic acid level of 29.2 µg/mL (reference range, 50 to 100 µg/mL), hemoglobin A_{1c} 5% (reference range, <5.7%), thyroid-stimulating hormone 0.4 mIU/L (reference range, 0.4 to 4.5 mIU/L), creatinine 1.36 mg/dL (reference range, 0.6 to 1.35 mg/dL), blood urea nitrogen (BUN) 11 mg/dL (reference range, 7 to



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Practice Points

- Monitor vital signs and order laboratory testing of blood counts, renal function, and lithium levels routinely for any patient who is taking lithium.
- Counsel patients about the possibility of lithium-induced symptomatic bradycardia as a routine addition to informed consent for lithium pharmacotherapy.
- Consider obtaining an electrocardiogram to monitor for lithium-induced changes in heart rate if the patient has a cardiac history or is age >40.

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Clinical Point

Bradycardia is defined as a heart rate <60 bpm; however, symptoms may not occur until the heart rate is <50 bpm



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Table

Recommended monitoring parameters for lithium

Prior to initiation of lithium	5 to 7 days after initiation or dosage change	Every office visit	Every 6 to 12 months
Vital signs ^a	Vital signs	Vital signs	Vital signs
Health history ^b			Health history
Current medications ^c		Current medications	Current medications
Birth control method		Birth control method	Birth control method
Laboratory studies: BMP, ^d CBC, TSH, urinalysis, pregnancy test ECG if cardiac history or age >40	Serum lithium level (obtained 12 hours after last oral dose)	Laboratory tests as indicated by signs or symptoms	Laboratory studies: BMP, lithium level, TSH, CBC ECG if cardiac history or age >40
Counseling: Risks of lithium toxicity, thyroid dysfunction, blood dyscrasia, bradycardia, tachycardia, teratogenicity, drug interactions			

^aIncludes heart rate, blood pressure, respiratory rate, weight, and temperature
^bIncludes history of kidney disease, thyroid impairment, and cardiovascular disease
^cScreen for NSAIDs, diuretics, and antihypertensive medications that may increase lithium levels
^dBMP includes creatinine, BUN, calcium, calculated GFR, and sodium for monitoring kidney function. Alternatively, order calcium and creatinine as separate tests, although this may be more expensive than a BMP

BMP: basic metabolic panel; BUN: blood urea nitrogen; CBC: complete blood count; ECG: electrocardiogram; GFR: glomerular filtration rate; NSAID: nonsteroidal anti-inflammatory drug; TSH: thyroid-stimulating hormone

25 mg/dL), a normal complete blood count, and an otherwise unremarkable chemistry panel. A urine drug screen is positive for marijuana. Other than discontinuation of lithium, no other medication changes are made.

Prior to starting lithium, Mr. C's weight was 165 lb, blood pressure was 129/89 mm Hg, respirations 22 breaths per minute, and HR 80 bpm. Over a 5-month pretreatment period, his HR readings ranged from 60 to 91 bpm, averaging 75 bpm. Over the 5-month period after lithium initiation, his HR readings ranged from 46 to 66 bpm, averaging 56 bpm. Over the 5-month period after discontinuing lithium, his HR readings range from 55 to 84 bpm, averaging 68 bpm. Use of the Naranjo Adverse Drug Reaction Probability Scale¹ indicates a possible relationship (4 of 13) between bradycardia and lithium use.

Bradycardia is defined as a HR <60 bpm; however, symptoms may not occur until the

HR is <50 bpm. Symptoms include fatigue, dizziness, lightheadedness, chest pain, shortness of breath, and syncope. The incidence of bradycardia during lithium treatment is unknown; it is considered a rare but serious adverse effect. A literature review reveals several case reports of bradycardia with lithium treatment,^{2,4} including symptomatic bradycardia after a single dose of lithium.⁵ Other possible causes of bradycardia include anorexia nervosa, hypothermia, hypothyroidism, hypoxia, infection, stroke, acute myocardial infarction, sedative or opiate use, increased vagal tone with exercise conditioning, and other medications including fluphenazine.⁶

Mr. C's symptoms may have been assumed to be secondary to several possible causes, including bradycardia, dehydration from poor oral intake, lithium toxicity, or an undiagnosed medical condition. The combination of nausea, dizzi-

Related Resource

- Meneguetti MG, Basile-Filho A, Martins-Filho OA, et al. Severe arrhythmia after lithium intoxication in a patient with bipolar disorder admitted to the intensive care unit. *Indian J Crit Care Med.* 2012;16(2):109-111.

Drug Brand Names

Benzotropine • Cogentin	Gabapentin • Gralise,
Divalproex extended-release • Depakote ER	Horizant, Neurontin
Fluphenazine • Permitil, Prolixin	Lithium • Eskalith, Lithobid
	Valproate • Depakote

ness, anorexia nervosa, blurred vision, and lightheadedness in a patient receiving lithium would certainly trigger a clinician's concern for lithium toxicity, but he (she) may not be aware of the risk of bradycardia as an adverse effect of lithium. Because Mr. C refused hospital transportation by EMS, discontinuing lithium appears to have been the safest option. Laboratory studies from the day after Mr. C presented to the clinic appeared to lessen the probability that lithium toxicity, hypothyroidism, valproate toxicity, type 2 diabetes mellitus, or infection had caused Mr. C's symptoms.

Although psychiatrists may be vigilant about monitoring for signs and symptoms of toxicity with lithium use by utilizing regular laboratory studies, they may not be as vigilant with monitoring vital signs at every patient visit (*Table, page 42*). This case demonstrates the importance of regular vital sign measurements to be able to detect this rare but serious adverse effect.

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