Chronic Digoxin Toxicity Leading to Institutionalization of an Elderly Woman

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INTRODUCTION

Cardiac glycosides were discovered by Sir William Withering more than 200 years ago and remain in use for pharmacologic treatment of atrial fibrillation and heart failure.[1] With the availability of alternative treatments and the lack of mortality benefit, prescribing of digoxin has decreased significantly over the past 20 years; however, toxicity-related mortality rates have not decreased to the same degree.[2] Nonetheless, digoxin remains widely used despite its narrow therapeutic window,[1-3] particularly as second-line therapy for patients with atrial fibrillation (with or without heart failure) for whom β-blockers are not an option because of intolerance or insufficient therapeutic effect.[4] In a recent study comparing digoxin and bisoprolol in patients with permanent atrial fibrillation and symptoms of heart failure, digoxin was associated with greater improvements in New York Heart Association functional class and fewer adverse events.[4] The recognition of patients who are at greater baseline risk for digoxin toxicity, as well as careful monitoring during therapy, is therefore important to ensure clinicians continue to prescribe digoxin only for patients who would safely benefit from it.

In clinical practice, serum concentration of digoxin is a surrogate marker for toxicity and adverse outcomes.[3] Independent post hoc analyses of the DIG (Digitalis Investigation Group) and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trials demonstrated a significant relationship between digoxin serum concentration and mortality.[3,5] Both analyses showed that concentration of 1.2 ng/mL or above was associated with increased risk of death.[3,5]

Digoxin serum concentrations and overall pharmacokinetics can be affected by patient-specific factors, such as renal function, muscle mass, and age, or by external factors, such as drug–drug interactions.[6,7] Although strong P-glycoprotein inhibitors and inducers affect the bioavailability of digoxin,[6] diuretics have also been shown to increase the risk of digoxin toxicity because of their associated risk of renal and electrolyte disturbances.[8] Loop diuretics are associated with the highest risk of digoxin toxicity, followed by thiazides and potassium-sparing diuretics.[8]

The incidence of digoxin toxicity is also markedly more prevalent among elderly patients than among younger people. The increased prevalence of toxicity is thought to be secondary to a decline in renal function and volume of distribution and an increase in the number of comorbidities.[7] Chronic toxicity in elderly patients consists of a well-documented syndrome of cardiac (lengthening of the PR interval, shortening of the QT interval, depression of the ST segment and t-wave, arrhythmias, bradycardia), gastrointestinal (anorexia, nausea, vomiting, diarrhea, abdominal pain), neurologic (hallucinations, paranoia, trigeminal neuralgia, depression, headaches, dizziness, malaise, fatigue), and visual manifestations, along with electrolyte disturbances.[1,7] Here, we report a case of chronic digoxin toxicity leading to institutionalization and later hospitalization of an elderly woman.

CASE REPORT

A 79-year-old woman with a variety of comorbidities, including chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus, stable coronary artery disease, stage G3bA1 chronic kidney disease (CKD; baseline serum creatinine 100–110 μmol/L), gout, atrial fibrillation, and heart failure with mildly reduced ejection fraction (40%–45%), presented to the emergency department of a large tertiary care centre.* In the emergency department, her family reported 4 days of confusion and generalized weakness, 1 to 2 months of progressive nausea and vomiting, weight loss of 15 kg, and low mood. Upon review of her provincial drug record and pharmacy medication list, her home medications were identified as acetylsalicylic acid 81 mg daily, metoprolol 12.5 mg twice daily, digoxin 0.125 mg daily, rosuvastatin 20 mg daily, rivaroxaban 20 mg daily, allopurinol 300 mg daily, nitroglycerin patch 0.2 μg/h daily, furosemide 60 mg daily, metformin

*The patient and her family provided informed consent for publication of this case report.

1000 mg twice daily, mirtazapine 15 mg at bedtime, tiotropium bromide 2 puffs inhaled daily, fluticasone–salmeterol 2 puffs inhaled daily, salbutamol 100 µg inhaled every 4 hours as needed, and pantoprazole 40 mg daily.

The patient had previously lived independently on her own, but 8 months before the current presentation, she moved to her son and daughter-in-law's home, where she lived for the next 4 months. Although she had several short admissions to hospital over this 4-month period, she had been coping at home until she was admitted to a rural hospital for urinary tract infection, COPD exacerbation, heart failure, and atrial fibrillation, about 4 months before the current presentation. Upon discharge from this 19-day admission, she was started on digoxin 0.125 mg for rate control. The specific reasons for the decision to initiate digoxin were not available. Unfortunately, 8 days after discharge, she was readmitted, with a similar presentation, for another 3 weeks. Because of ongoing low blood pressure during this admission, medication changes at discharge included discontinuation of ramipril 1.25 mg daily (which she had been taking for only 3 weeks) and initiation of furosemide 20 mg daily. Her heart rate was 101/min on admission for the 3-week stay, and her renal function at that time was stable, with serum creatinine of 103 µmol/L. One month after discharge from this hospital stay, the patient's furosemide was increased from 20 mg to 60 mg daily, with no further monitoring of her renal function.

Within 1 month, the patient demonstrated rapid decline in memory and mobility at home and was moved by her family to a supportive living facility. Over the 3-month period since moving to supportive living, the patient was noted to have reduced appetite, with limited oral intake, which did not improve with a trial of ondansetron. She also experienced low mood, and an adjustment disorder was diagnosed, secondary to her increasing functional limitation. Worsening of her mobility and memory led to transfer to a long-term care facility approximately 3 weeks before the current presentation. Mirtazapine had been prescribed 1 week before the current admission, with no demonstrated benefit, as reported by her family. In the last few days before admission, the family had noted rapid worsening of dehydration, weakness, and confusion, which culminated in altered level of consciousness.

When she presented to the emergency department, the patient weighed 70 kg and was found to be bradycardic (heart rate 55/min), hypotensive (blood pressure 96/48 mm Hg), and afebrile. Telemetry monitoring in the emergency department revealed further bradycardic events, with her heart rate intermittently dropping to 30–40/minute, as well as bigeminy alternating with sinus bradycardia interrupted by frequent premature ventricular complexes. Her score on the Glasgow Coma Scale was calculated as 10 (E3V3M4), and results of the examination were otherwise significant for findings of clinical hypovolemia and anuria.

Initial laboratory investigations were significant for leukocytosis, with white blood cell count of 11.5×10^9/L and neutrophil count of 9×10^9/L; acute kidney injury, with serum creatinine of 841 µmol/L, from a baseline of 110 µmol/L; hyperkalemia, with presenting potassium of 6.2 mmol/L; anion gap metabolic acidosis, with pH of 7.14, urea of 26.5 mmol/L, bicarbonate of 14 mmol/L, and anion gap of 19 mmol/L; lactate level of 6.2 mmol/L; and hypoglycemia, with glucose level of 2.1 mmol/L. Urinalysis showed isolated pyuria, and chest radiography demonstrated a new right lower lobe consolidation. Electrocardiography showed accelerated junctional rhythm with occasional premature ventricular complexes, a previous inferior infarct, poor R wave progression, and low voltages. The digoxin serum concentration was markedly elevated, at 4.8 nmol/L; no previous digoxin concentration had been recorded in the electronic medical record since initiation of this medication. Her most recent laboratory testing had been approximately 3 months before this presentation.

Aggressive medical management was pursued consistent with goals of care ("do not resuscitate"), including volume resuscitation, shifting of potassium, empiric antimicrobials for infection (pneumonia versus urinary tract infection), and initiation of telemetric cardiac monitoring, with the family's consent. Poison control was activated, and 3 vials (120 mg) of digoxin immune fab were administered. Hemodialysis was deemed not to be consistent with the patient's goals of care. Home rate-modifying, antihypertensive, and nephrotoxic medications (metoprolol, nitroglycerin patch, and furosemide, respectively) were held, in addition to her anticoagulant, rivaroxaban.

During the 9-day admission at our facility, she received supportive care and made a dramatic recovery. Within days, the bradycardia and hypotension resolved, with subsequent resolution of her acute kidney injury, acidosis, and hyperkalemia. Her appetite, mood, and weakness improved with the resolution of her nausea and vomiting, and her family noted that her overall condition and cognition recovered to levels not seen before her move to supportive living 4 months prior. She worked with physiotherapy and occupational therapy and returned to baseline mobility with a gait aid. Her polypharmacy was addressed, and she left the hospital with discontinuation of digoxin, metformin, furosemide, nitroglycerin patch, and mirtazapine. The dosages of her other home medications were adjusted to take into account her baseline CKD. She was discharged home to her previous supportive living environment, instead of long-term care.

For several reasons, we attributed this patient's overall clinical presentation and institutionalization to chronic digoxin accumulation. Her calculated score on the Naranjo Adverse Drug Reaction Probability Scale[9] was 8, and the temporal sequence of events fit with the characteristics of chronic digoxin toxicity. Dose escalation of furosemide 2 months after initiation of digoxin, compounded by her

baseline CKD, likely triggered the cycle of toxicity that was further exacerbated by digoxin-induced nausea and vomiting, resulting in dehydration, worsening of renal function, and impairment of function and cognition necessitating placement in long-term care. The lack of renal function and therapeutic drug monitoring after therapy initiation also contributed to significant toxicity in this particular case. It does not appear that digoxin toxicity was ever considered as contributing to the patient's decline: in the 5 months since initiation of this drug, the patient did not undergo any measurement of digoxin serum levels.

DISCUSSION

This case of institutionalization and severe morbidity of a 79-year-old woman with symptoms of chronic digoxin toxicity highlights not only the clinical signs and symptoms of this type of toxicity but also the critical nature of drug monitoring in elderly patients for whom digoxin is initiated. Serum concentration monitoring can help to prevent toxicity associated with concomitant use of digoxin and diuretics and to reduce the risk of chronic accumulation. When digoxin is initiated in elderly patients, careful consideration should be given to the patient's weight, age, and renal function.[10]

Adequate drug monitoring to identify patients who stand to benefit most from digoxin withdrawal is even more crucial in light of the fact that stopping digoxin can be associated with adverse outcomes. Data from the PROVED (Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin)[11] and RADIANCE (Randomized Assessment of the Effect of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme)[12] studies, as well as an analysis of the OPTIMIZE-HF registry,[13] suggest that discontinuing digoxin in ambulatory patients with established heart failure with reduced ejection fraction is associated with worsening of heart failure symptoms and functional capacity and increases in rates of hospital admission for heart failure. However, 2 of these studies[11,12] excluded patients with severe CKD, which was a significant risk factor for digoxin toxicity in our patient and should be considered in the risk–benefit calculus when deciding to discontinue digoxin therapy.

To our knowledge, this is the first published report of chronic digoxin toxicity leading to institutionalization. Altered level of consciousness or drug-induced confusion may be the only symptom of digoxin toxicity in some elderly patients, and central nervous system effects can occur even when digoxin levels are within normal range.[14] There is limited evidence to support withdrawal of maintenance digoxin in elderly patients entering institutional living.[15] However, in a small study, 12 of 14 patients living in a long-term care facility tolerated discontinuation of digoxin, which suggested a high prevalence of polypharmacy.[15]

CONCLUSION

In elderly patients with atrial fibrillation or heart failure, we suggest consideration of an alternate agent instead of digoxin and deprescribing if possible. Alternatively, careful drug monitoring is essential, with an emphasis on clinical assessment in addition to measurement of drug levels, given that the latter can help to rule in digoxin toxicity but may be an unreliable rule-out test. We suggest that clinicians maintain a high index of suspicion for digoxin toxicity in elderly patients with renal impairment who are taking this drug and who present with confusion or altered level of consciousness, and that they consider ordering routine digoxin levels in this scenario.

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