

Case Report

Digoxin Toxicity Precipitated by Clarithromycin Use: Case Presentation and Concise Review of the Literature

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ABSTRACT

We present a case of digoxin toxicity in the context of dehydration, renal dysfunction and concomitant use of the macrolide antibiotic, clarithromycin, which is known to inhibit P-glycoprotein-mediated efflux mechanisms of digoxin. A focused review of the literature is presented. Health care providers need to be vigilant of this mechanism of drug–drug interaction, which is also relevant to other commonly used cardiovascular drugs.

RÉSUMÉ

Nous présentons un cas d'intoxication à la digoxine dans un contexte de déshydratation, de dysfonction rénale et d'utilisation concomitante d'antibiotiques macrolides, la clarithromycine, qui est connue pour inhiber les mécanismes d'efflux de la digoxine par l'intermédiaire de la glycoprotéine P. Une analyse documentaire ciblée est présentée. Les dispensateurs de soins doivent être vigilants à ce mécanisme d'interactions médicamenteuses, qui est aussi applicable à d'autres médicaments cardiovasculaires communément utilisés.

A previously well-functioning 83-year-old man with a past history of hypertension, dyslipidemia, myocardial infarction, left ventricular dysfunction, and chronic obstructive pulmonary disease presented to hospital with a recent history of fatigue, dyspnea on exertion, cough, nausea, loss of appetite, and lightheadedness. Three days prior to his presentation, the patient had been started on clarithromycin 500 mg PO twice daily for the treatment of possible pneumonia. His cardiac medications included digoxin 0.125 mg PO daily, spironolactone 25 mg PO once daily, captopril 25 mg PO twice daily, pravastatin 40 mg PO daily, isosorbide mononitrate 30 mg PO daily, furosemide 60 mg PO daily, bisoprolol 2.5 mg PO daily, and potassium 20 mmol PO daily. Due to severe nausea, the patient presented to the emergency department following completion of his fifth dose of clarithromycin. On examination, he appeared unwell. He was afebrile. His blood pressure and heart rate were 124/50 mm Hg and 68 beats per minute (supine) and 105/40 mm Hg and 82 beats per minute (standing), respectively. His respiratory rate was 16/min with an oxygen saturation

of 99% (room air). Cardiorespiratory examination did not show signs of decompensated heart failure (HF). Blood tests demonstrated a white cell count of $13.6 \times 10^9/L$, potassium 5.2 mM, urea 15.8 mM, creatinine 184 μM (3 weeks earlier: urea 12.3 [reference 2.5–8.2] mM, and creatinine 116 [reference 65–120] μM), and digoxin levels of 4.6 nM (5 hours postdose) and 4.7 nM (18 hours postdose). His electrocardiogram showed normal sinus rhythm, complete right bundle branch, and left anterior hemiblock and evidence of prior anteroseptal and inferior infarctions (no significant changes from previous electrocardiogram).

The presentation of this patient was consistent with digoxin toxicity in the context of dehydration, a recent onset of renal dysfunction, and concomitant use of the macrolide antibiotic clarithromycin, which is known to inhibit P-glycoprotein-mediated efflux mechanisms of digoxin.¹ Both drugs were stopped immediately. In addition, medications that could raise serum potassium levels, including spironolactone, captopril, and potassium supplements, were discontinued on a temporary basis. The patient was rehydrated. Ventricular extrasystoles were observed during monitoring. The patient was admitted to hospital and improved clinically. Blood tests on day 2 of hospitalization showed a digoxin level of 3.2 nM, urea 16.9 mM, creatinine 154 μM , and potassium 3.9 mM. His serum creatinine level subsequently returned to normal and his medications were optimized. He was discharged from hospital

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uneventfully 10 days later (urea 11.4 mM and creatinine 103 μ M).

Discussion

Digoxin is a commonly used cardiac glycoside for the treatment of HF and for controlling ventricular response in atrial fibrillation. Digoxin is a substrate for P-glycoprotein, which is an adenosine triphosphate (ATP)-dependent multidrug efflux transporter located on the luminal surface of epithelial cells of the small intestine, bile canalicular membrane of the liver, renal proximal tubules, and endothelial cells that form the blood-brain and blood-testes barriers.¹ Most of the body load of digoxin is eliminated by the kidney unchanged by both glomerular filtration and tubular secretion. In this case, the newly developed renal insufficiency affected glomerular filtration rate (GFR), whereas the clarithromycin inhibited the tubular secretion of the cardiac glycoside. When these 2 drugs are combined, it is reasonable to decrease digoxin dose by half with careful therapeutic drug monitoring.

Notably, because amiodarone¹ and the newer antiarrhythmic drug, dronedarone, (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022425s007lbl.pdf) are both inhibitors of P-glycoprotein, they share the same mechanism of interaction with digoxin. In addition, spironolactone (http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/012151s062lbl.pdf) can elevate digoxin levels by reducing tubular secretion and might have been a contributing factor to digoxin toxicity in our patient, although the disproportional increase in creatinine vs urea would suggest a reduced GFR being a prominent factor other than drug–drug interactions. The interaction between digoxin and clarithromycin, as well as other macrolide antibiotics, has been reported.^{2–4}

In 7 elderly patients who received chronic digoxin therapy, Zapater et al.² conducted a prospective observational study to evaluate potential interaction between digoxin and clarithromycin. These investigators measured digoxin levels before and after concurrent clarithromycin use and observed a significant reduction in calculated digoxin clearance following 4–7 days of clarithromycin therapy, with an elimination half-life that was 82% longer.² In 8 digoxin-treated HF patients, Tanaka et al.³ studied the effect of clarithromycin on steady-state digoxin levels and reported an increase in digoxin level during concomitant administration of clarithromycin (which was also depen-

dent on the dose of clarithromycin). Specifically, with an oral dose of clarithromycin 400 mg/day, there was an approximately 70% increase in digoxin concentration.

In a 15-year, population-based, nested case-control study in Ontario, Gomes et al.⁴ evaluated the association between hospitalization for digoxin toxicity and recent use of macrolide antibiotics. These investigators observed that a recent exposure to clarithromycin was associated with the highest risk of digoxin toxicity, with an adjusted odds ratio of 14.8, among the individual macrolide antibiotics studied.⁴ The results of this study underscore the potentially serious consequences of this drug–drug interaction.

With the advent of newer anticoagulants, in particular, dabigatran, it is anticipated that an increasing number of patients will be switched from warfarin to this reversible direct thrombin inhibitor, which is also a substrate of P-glycoprotein with moderate affinity and is dependent on transport-mediated renal excretion.⁵ Physicians need to be aware that drugs like clarithromycin, amiodarone, and dronedarone affect the transport proteins involved in renal secretion and therefore will affect the levels of many drugs, such as digoxin and dabigatran, that depend on renal elimination.^{1,5}

Disclosures

The authors have no conflicts of interest to disclose.

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