Digoxin toxicity precipitated by *Helicobacter pylori* eradication therapy

Introduction

Although digoxin was introduced into clinical practice more than 200 years ago (Vamos et al, 2015), it is still widely used in patients with atrial fibrillation and left ventricular failure (Ziff and Kotecha, 2016). Inadvertent digoxin toxicity can arise as a result of its narrow therapeutic window and the potential to interact with other drugs.

The interaction of macrolides with digoxin has been reported and the risk seems to be higher in the elderly and with clarithromycin use (Zapater et al, 2002; Lee et al, 2011). Omeprazole has also been reported to interact with digoxin, albeit not frequently leading to digoxin toxicity. Prescribing physicians should be aware of the potential for drug–drug interactions prompting close monitoring of drug levels or use of an alternative medication.

Discussion

The interaction between macrolides and a number of drugs has been largely described, but this case serves as an important clinical reminder of a severe drug–drug interaction which may have been avoided. Clarithromycin decreases digoxin secretion by inhibiting P-glycoprotein-mediated transport (Eberl et al, 2007). Other drugs known to alter P-glycoprotein activity include omeprazole, verapamil, dilitiazem, quinidine, amiodarone and itraconazole.

Dr Roberta Callus, Locum Consultant, Department of Medicine, Mater Dei Hospital, Msida MSD 2090 Malta

Dr Tiziana Felice, Resident Specialist, Department of Cardiology, Mater Dei Hospital, Malta

Dr Deborah Balzan, Basic Specialist Trainee, Department of Medicine, Mater Dei Hospital, Malta

Dr Lara Delicata, Resident Specialist, Department of Medicine, Mater Dei Hospital, Malta

Correspondence to: Dr R Callus (robertacallus@yahoo.co.uk)

During clarithromycin use, the risk of digoxin toxicity is four times greater than with erythromycin or azithromycin (Gomes et al, 2009). Substitution of clarithromycin with azithromycin in triple therapy regimens lead to similar levels of eradication (Khoshnood et al, 2014). Macrolides also alter the digoxin-metabolising gut flora, particularly *Eubacterium lentum*, causing an increase in digoxin concentration in susceptible individuals (Kiran et al, 2004).

Digoxin toxicity can be avoided by monitoring serum digoxin levels before and during macrolide therapy. Pre-emptive reduction of digoxin dose by approximately 30–50% during macrolide use should be considered, or alternative antibiotic options may be considered. Evidence is lacking regarding the use of probiotics to prevent alterations in digoxin-metabolising gut flora as a result of macrolide use.

Digoxin is not eliminated by extracorporeal measures because of its large molecular weight (Mowry et al, 2016). Haemodialysis may still be indicated for intractable hyperkalaemia or acute kidney

CASE REPORT

An 80-year-old woman with a background of hypertension, atrial fibrillation, left ventricular failure and chronic kidney disease stage 3b with an atrophic right kidney on renal imaging, was being investigated for chronic iron deficiency anaemia. An oesophagogastroduodenoscopy showed evidence of *Helicobacter pylori*, for which she was prescribed eradication therapy with clarithromycin 500 mg twice daily, amoxicillin 1 g twice daily and omeprazole 20 mg twice daily (increased from her previous omeprazole dose of 20 mg daily). She was advised to take the two antibiotics for 14 days. She was also receiving digoxin 0.125 mg daily for heart rate control together with warfarin, a diuretic and an angiotensin-converting enzyme inhibitor. Serum digoxin concentration before starting eradication therapy was between 1.5 and 2.0 ng/ml (within the therapeutic range of 0.9–2.0 ng/ml).

Two weeks after the oesophagogastroduodenoscopy and on completion of eradication therapy, she presented to the emergency department with epigastric discomfort, nausea, diaphoresis, blurred vision and light-headedness. Her heart rate was 124 beats per minute and blood pressure was 153/78 mmHg with no significant postural drop. She had a respiratory rate of 18 breaths per minute with oxygen saturations of 99% on room air and she was afebrile. On auscultation, she had normal heart sounds with no signs of fluid overload. Abdominal examination revealed mild epigastric tenderness with no rebound or guarding and bowel sounds were present.

An electrocardiogram showed junctional tachycardia at a rate of 120 beats per minute with a right bundle–branch block pattern and significant reverse tick ST segment depression (*Figure 1*). An electrocardiogram done 3 weeks before admission showed rate-controlled atrial fibrillation with incomplete right bundle–branch block. Cardiac monitoring revealed non-sustained bidirectional ventricular tachycardia and runs of bradycardia (*Figure 2*).

Initial blood investigations showed an acute kidney injury (serum creatinine of 163 umol/litre (normal range 45–84 umol/litre) from a baseline of 115 umol/litre) with associated hyperkalaemia (serum potassium of 6.04 mmol/litre). Magnesium and calcium levels were 1.02 mmol/litre (normal range 0.65–1.05 mmol/litre) and 2.13 mmol/litre (normal range 2.05–2.60 mmol/litre) respectively. Serum digoxin level was markedly raised at 9.9 ng/ml (normal range 0.9–2.0 ng/ml). Amylase was within normal limits at 38 U/litre. Chest X-ray showed clear lung fields with an increased cardiothoracic ratio.

The patient was admitted to the coronary care unit and 200 mg DigiFab (digoxin-specific antigen binding fragment) was administered intravenously. She was monitored in the coronary care unit for bradyarrhythmias, but temporary pacing was not required during her inpatient stay. She was subsequently discharged home off digoxin but required carvedilol for heart rate control. On discharge her creatinine level was 130 umol/litre with normal electrolytes.

Figure 1. Electrocardiogram on admission showing junctional tachycardia with a right bundle–branch block pattern and significant reverse tick ST segment depression.

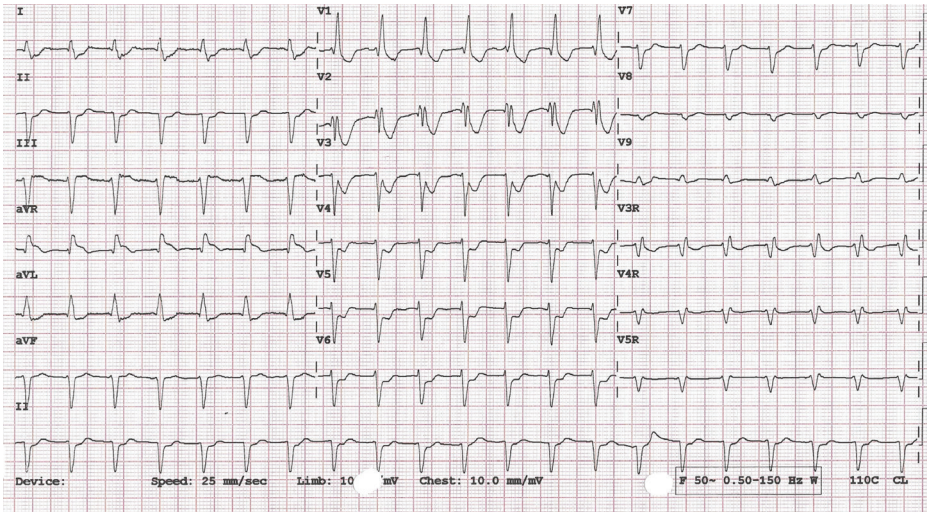
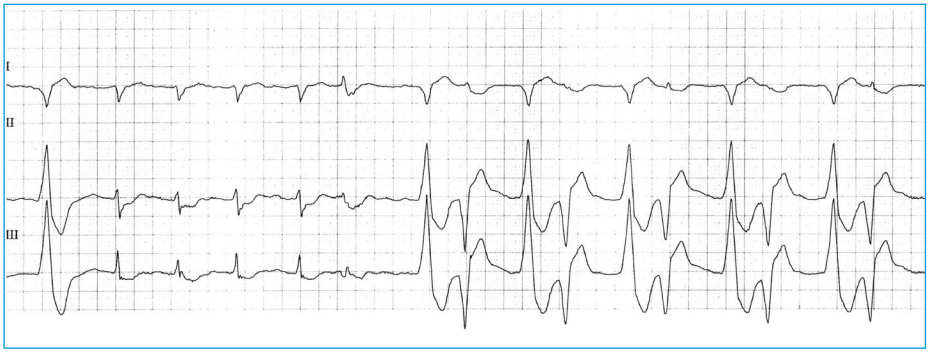


Figure 2. Non-sustained bidirectional ventricular tachycardia – a hallmark of severe digoxin toxicity.



injury. The decision to treat with antibody fragments primarily relies on the presence of hyperkalaemia, life-threatening or haemodynamically unstable arrhythmia, renal failure, and confusion or end-organ dysfunction from hypoperfusion (Bateman, 2004).

Digoxin-specific antigen binding fragment has a half-life of 19–30 hours, increasing to >130 hours in patients with renal failure (Ujhelyi and Robert, 1995). Once administered, serial digoxin level monitoring is not routinely recommended, unless a serum free digoxin assay is available. Indeed, the measured total serum digoxin level tends to increase despite a free digoxin level approaching zero.

This case highlights the importance of physician awareness and knowledge regarding the interaction of commonly prescribed drugs. Monitoring and readjusting digoxin dose before and during concomitant clarithromycin use could have avoided drug toxicity and its resultant sequelae. **BJHM**

Bateman DN. Digoxin-specific antibody fragments: how much and when? Toxicol Rev. 2004;23(3):135–143. https://doi.org/10.2165/00139709-200423030-00001

Eberl S, Renner B, Neubert A et al. Role of p-glycoprotein inhibition for drug interactions: evidence from in vitro and pharmacoepidemiological studies. Clin Pharmacokinet. 2007;46(12):1039–1049. https://doi.org/10.2165/00003088-200746120-00004

Gomes T, Mamdani MM, Juurlink DN. Macrolide-induced digoxin toxicity: a population-based study. Clin Pharmacol Ther. 2009 Oct;86(4):383–386. https://doi.org/10.1038/clpt.2009.127

Khoshnood A, Hakimi P, Salman-Roghani H, Reza Mirjalili M. Replacement of clarithromycin with azithromycin in triple therapy regimens for the eradication of Helicobacter pylori: A randomized clinical trial. J Med Life. 2014 Jun 15;7(2):254–259.

LEARNING POINTS

- Digoxin levels should be closely monitored when co-administering macrolides or other drugs known to cause drug–drug interactions since dose adjustments may be required.
- Consider an alternative drug if possible to minimize drug–drug interactions.
- Total digoxin levels are unreliable after administering digoxin-specific antigen binding fragment as they measure both bound and unbound drug levels despite a reduction in 'free' digoxin levels.
- In a patient with digoxin toxicity and renal dysfunction, cardiac monitoring should continue for a minimum of 72 hours because of the prolonged elimination of digoxin-specific antigen binding fragment.
- Extracorporeal treatments for digoxin toxicity are not advocated because of the large molecular size of the drug, but dialysis is at times required in the setting of acute kidney injury or intractable hyperkalaemia.

Kiran N, Azam S, Dhakam S. Clarithromycin induced digoxin toxicity: case report and review. J Pak Med Assoc. 2004 Aug;54(8):440–441.

Lee CYW, Marcotte F, Giraldeau G, Koren G, Juneau M, Tardif JC. Digoxin toxicity precipitated by clarithromycin use: case presentation and concise review of the literature. Can J Cardiol. 2011 Nov;27(6):870.e15–870.e16. https://doi.org/10.1016/j.cjca.2011.06.006

Mowry JB, Burdmann EA, Anseeuw K et al; EXTRIP Workgroup. Extracorporeal treatment for digoxin poisoning: systematic review and recommendations from the EXTRIP Workgroup. Clin Toxicol. 2016 Feb 07;54(2):103–114. https://doi.org/10.3109/15563650.2015.1118488

Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. Clin Pharmacokinet. 1995 Jun;28(6):483–493. https://doi.org/10.2165/00003088-199528060-00006

Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. Eur Heart J. 2015 21;36(28):1831-8. https://doi.org/10.1093/eurheartj/ehv143

Zapater P, Reus S, Tello A, Torrús D, Pérez-Mateo M, Horga JF. A prospective study of the clarithromycin-digoxin interaction in elderly patients. J Antimicrob Chemother. 2002 Oct 1;50(4):601–606. https://doi.org/10.1093/jac/dkf176

Ziff OJ, Kotecha D. Digoxin: the good and the bad. Trends Cardiovasc Med. 2016 Oct;26(7):585–595. https://doi.org/10.1016/j.tcm.2016.03.011