Case Report

Digoxin and Symptomatic Bradyarrhythmia: the 'demon' or a 'red herring'.

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Abstract

Digoxin toxicity has been implicated in all forms of cardiac arrhythmias with the notable exception of Mobitz II atrioventricular block, which is very rare. The manifestation is quite variable, ranging from being asymptomatic to gastrointestinal, cardiac, and neurologic symptoms. The manifestations can be protean in the elderly, the most vulnerable group, where degenerative cardiac conduction system diseases add another layer of intrigue by providing an intrinsic substrate for cardiac dysrhythmia. This is in addition to age-related alteration of digoxin pharmacokinetics, use of multiple medications, chronic conditions, and electrolyte derangement, all of which increase the propensity for digoxin toxicity. We present a case of various atrioventricular conduction blocks in a septuagenarian following the use of digoxin.

Keywords: Digoxin; Bradycardia; Atrioventricular Block; Complete Heart Block; Syncope.

Introduction

Despite rapid advancements in the management of heart failure with newer and more effective medications and other treatment modalities, digoxin has relatively maintained a place in the armamentarium of drug treatment of chronic heart failure for over three centuries. The major drawback to digoxin is its narrow therapeutic window and by extension its relatively high propensity to adverse drug reaction (ADR). This is particularly so in the elderly, the same age group that harbours the largest number of people with chronic heart failure and atrial fibrillation and in whom digoxin is commonly prescribed.

Digoxin acts by inhibiting membrane-bound Na^+-K^+-ATPase, and blockade off Na^+ efflux from the cell. As a result, the Na gradient required for the efflux of Ca is abolished, resulting in the accumulation of intracellular Ca in the sarco/endoplasmic reticulum Ca^{2+} adenosinetriphosphate-2a (SERCA2a)[1]. The increased intracellular Ca^{2+} then mediate sex citation-contraction coupling, giving rise to the ionotropic effect of digoxin. The cardiac manifestations of digoxin toxicity are a direct extension of its mechanism of action. By increasing the duration of cardiac action potential (phase 0 and phase 4), digoxin not only reduces the heart rate (that may degenerate to dangerous bradyarrhythmia) but also predisposes to arrhythmogenesis because of increased automaticity. In digoxin toxicity, conduction block and increased automaticity occurring in the same setting results in paroxysmal atrial tachycardia with conduction block, its classic rhythm.[2]

The elderly aremore prone to digoxin toxicity for a variety of reasons. Age-related reduction in the volume of distribution (decreased muscle

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mass/increased fat mass), a decline in renal function and hypoalbuminemia significantly impact the pharmacokinetics of digoxin. The use of medications for other comorbidities resulting in electrolyte derangements (hypokalemia and hypomagnesaemia from diuretics) and drug-drug interaction potentiates the occurrence of digoxin toxicity in the elderly. [3] Other factors include chronic conditions including ischemic heart disease, chronic obstructive airway disease and hypothyroidism; and probably the highly conjectured age-related increase in end-organ sensitivity to digoxin. [4]

The clinical manifestation of digoxin toxicity is variable and can be protean especially in the elderly. In acute toxicity, gastrointestinal symptoms of nausea, anorexia and vomiting, and cardiac manifestations dominates, whereas malaise, weakness and visual disturbances predominate in chronic toxicity. Historically, the most common cardiac manifestation of digoxin toxicity is paroxysmal ventricular beats, occurring in a single form, multiform and bigeminal patterns; followed by various forms of heart block. [5]In the series reviewed by Irons and Orgain, paroxysmal atrial tachycardia (PAT) and junctional tachycardia occurred in 13% each while atrial fibrillation (AF) and ventricular tachycardia (VT) were each recorded in 10% of cases.[5]

Differentiating digoxin-induced cardiac dysrhythmia from age-related conduction system disease can be quite challenging in the elderly. Adding another layer of intrigue is the fact that the same patient can manifest different forms of dysrhythmia on re-exposure to the same dose of a given cardiac glycoside. [6] We present a case of various forms of heart block in a septuagenarian following exposure to digoxin.

Case

A septuagenarian was referred to the cardiac outpatient clinic on account of efforts intolerance, palpitation, and lightheadedness. There was no history of chest pain, cough or leg swelling, and there were no gastrointestinal symptoms. He had a trans-vesical prostatectomy for bladder outlet obstruction at the University of Maiduguri teaching hospital three months before the onset of cardiac symptoms. While attending the urology clinic for follow up, an ECG was requested. Five days prior to his follow-up date, he presented to a private hospital with the symptoms, for which he was given digoxin and furosemide, and he was referred to the cardiac clinic.

He had three episodes of syncope, each lasting a couple of minutes and decided to suspend digoxin and furosemide before attending the cardiac clinic. He has been hypertensive for many years with good blood pressure control on lisinopril. He is not diabetic and has not had myocardial infarction, stroke, or transient ischemic attack in the past. He did not smoke a cigarette or drink alcohol. Pre- and post-operative biochemistry were within normal limits.

When examined, he was found to be a pleasant elderly man and was not in distress. He was not febrile or pale, and there was no pedal oedema. His resting pulse was regular at 36 bpm, with a large but non-collapsing character, and all peripheral pulses were present and synchronous. The arterial wall was thickened with a blood pressure of 170/67mm Hg (sitting position, right arm, diastolic BP recorded as phase 4 of Korotkoff sound because of persistent systole). Jugular venous pressure was 7cm of H_2O and apex was un-displaced but heaving. There are no features of aortic or other valvar heart dysfunction. Chest and abdominal examinations, as well as other systems, are essentially normal. A diagnosis of symptomatic bradycardia was made.

The initial resting ECG obtained from the urology clinic showed 3:1 atrioventricular block (AVB) with sinus and ventricular rates of 88 beats and 29 beats per minute respectively (figure 1). A second ECG (figure 2) obtained during cardiac consultation revealed a ventricular rate of 42 beats per minute with a combination of sinus 1:1 conduction (two cycles), 2:1 AVB (two runs) and 3:1 AVB (three runs). Both ECGs (figure 1 and figure 2) showed a marginal increase in QTc (449ms and 466ms, respectively). There were no convincing features of previous myocardial infarction or chamber hypertrophy/enlargement.

Echocardiography revealed diastolic dysfunction and degenerative aortic and mitral valve morphology. Left ventricular systolic function was normal, and there was no area of wall motion abnormality or thinning. Holter ECG and assay for serum digoxin was not available. Results of thyroid and renal function, as well as electrolytes, were normal. He was maintained on 10mg of lisinopril for hypertension and conservatively followed up off digoxin. He declined referral to a Centre with electrophysiology study capability for further evaluation. However, remained asymptomatic, and ECGs during two successive follow-ups revealed sinus rhythm (figure 3).

He defaulted follow up and was rushed to the cardiac clinic following an episode of syncope with faecal and urinary incontinence while trying to cross the road. ECG revealed third-degree AVB (figure 4) and requested to be referred for a permanent cardiac pacemaker. Because of financial constraints, he could only afford a VVI, which was implanted at a private hospital. He maintained regular follow up at the cardiac clinic and has been free of symptoms.

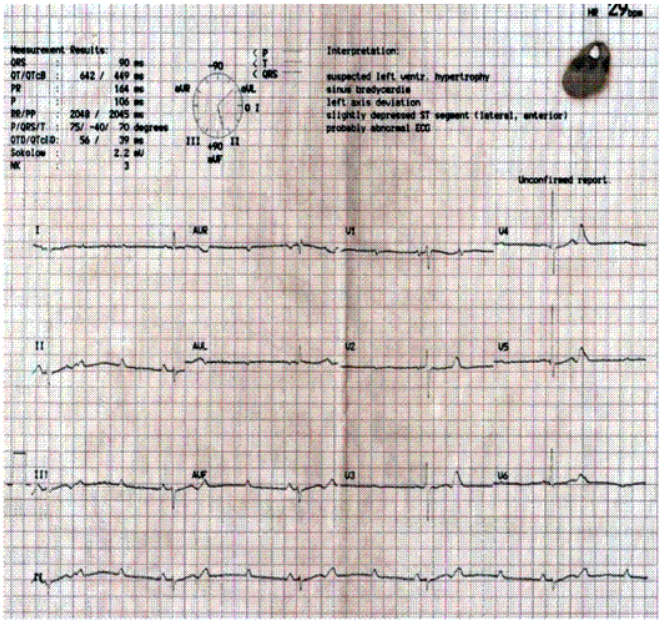

Figure 1: 3:1 atrioventricular block (AVB) with a sinus and ventricular rates of 88 beats and29 beats per minute respectively

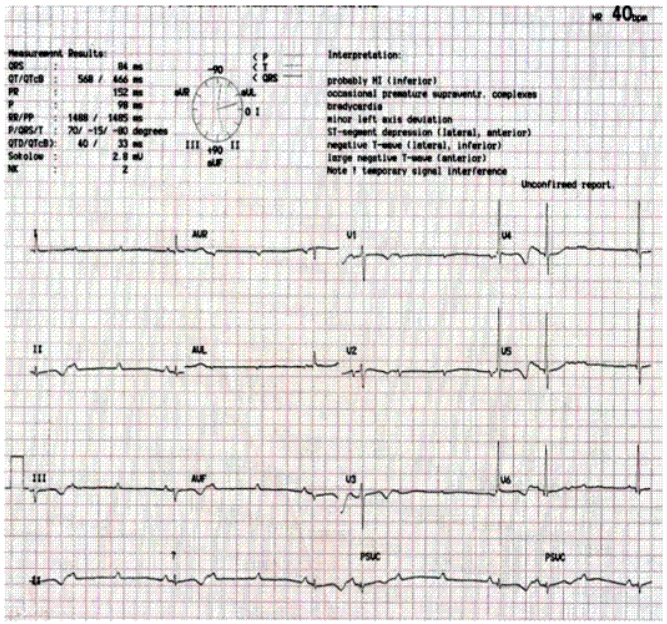

Figure 2: Ventricular rate of 42 b.p.m. with combinations of 1:1 conduction and AVB (single-run of 2:1 and three runs of 3:1 AVB)

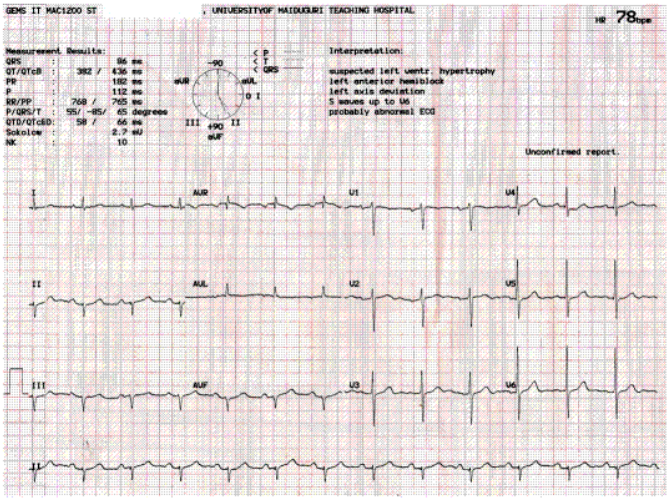

Figure 3: Sinus rhythm with a rate of 78 beats per minute

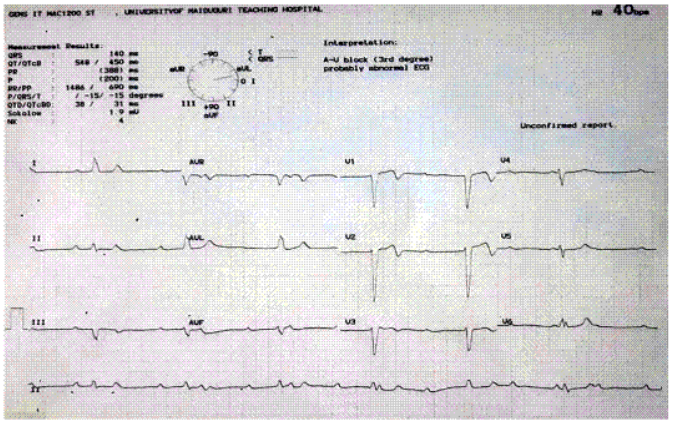

Figure 4: Complete heart block

Discussion

Our case illustrates the challenges bedevilling management of patients with cardiac arrhythmias in developing countries ranging from misdiagnosis, lack of basic requisite diagnostic tools, inappropriate (and life-threatening) management, and virtual lack of life-saving treatments. This is reminiscent of what obtains in many countries of sub-Saharan Africa.

Digoxin could result in any form of cardiac dysrhythmias with the notable exception of Mobitz II block which is rare. The most common bradyarrhythmia linked to digoxin toxicity is first-degree heart block (reported in 12% of cases) and, second and third-degree AVB, each reported in 11% per cent of cases. [5] Our patient displayed advanced AVB and complete heart block at various times, eventually needing a cardiac pacemaker.

Digoxin toxicity is common in the elderly for a variety of reasons bordering on altered pharmacokinetics,

polypharmacy with the heightened propensity for drug-drug interactions, electrolyte derangements and the inherent age-related degenerative cardiac conduction system disease. In Lev's disease, a form of progressive cardiac conduction disease, fibro-fatty degeneration of the aortic sinuses, central fibrous body, ventricular septum, mitral annulus, the bundle of His and Purkinje fibre as described, resulting in progressive lengthening of the AV conduction time. [7] However, where conduction occurred in our patient (during sinus rhythm and AVB), the PR interval was within normal limits (figure 2).

The various degrees of AVB experienced and the temporal relation to digoxin exposure and eventual restoration of sinus rhythm following discontinuation contextually implicates digoxin as the culprit. The half-life of digoxin in healthy individuals ranges from 26 to 45 hours, which can be substantially increased in the setting of renal failure. [8] However, our patient had a normal renal function. It is implausible to implicate digoxin for the complete heart block developed many months after it has been stopped, where it can at most be contextually described as a 'red-herring' and not the 'demon'. Notwithstanding, the threshold for diagnosing digoxin toxicity in the elderly manifesting with the clustering of symptoms and ECG abnormalities observed in our patient should be below. In the presence of diastolic dysfunction, left ventricular (LV) filling becomes more dependent on the atrial kick. Sustaining physiologic LV filling will require dual-chamber cardiac pacing. The patient could only afford a VVI, making pacemaker syndrome a potential complication to be on the lookout for.

The management of this patient brings to fore the many challenges experienced in the care of patients with cardiac arrhythmias in our centres. First, the prescription of digoxin would be difficult to substantiate since he was not in atrial fibrillation and echocardiography showed normal LV systolic function. Secondly, serum digoxin level, an essential component of the evaluation that would guide appropriate therapy was not available. Thirdly (and not least), the non-availability of digoxin-Fab is required for life-threatening hemodynamically compromising situations.

Conclusion

The case highlights two interwoven issues:1) the challenging task of diagnosing digoxin toxicity in the elderly where the manifestation is rather protean, and cardiac substrate for digoxin-related dysrhythmias, exists; 2) non-availability of requisite facilities for the evaluation of patients with cardiac dysrhythmia. For the former, diligent clinical evaluation, while lowering the threshold for diagnosing digoxin toxicity will improve the diagnostic yield. In terms of facilities, it is hoped that the awakening is being championed by the African Heart Rhythm Association (a working group of the Pan African Society of Cardiology, PASCAR) in improving training and care of patients with cardiac rhythm disorders will provide succour.

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