Rare Interaction of Warfarin and Digoxin in a Case of Digoxin Toxicity

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Abstract

Warfarin is known to interact with many drugs and can lead to serious consequences.

We report a case of 52 years old female patient from Himachal Pradesh. During hospital stay patient developed coagulopathy in form of INR above 10 and bradycardia with ventricular rate on ECG with digoxin level of 3.76 ng/ml. In this way digoxin toxicity was confirmed and it was considered as cause of coagulopathy after ruling out interactions of warfarin.

Introduction

Drug interaction with warfarin is a common cause of raised INR or coagulopathy. But an interaction of digoxin toxicity with warfarin leading to raised INR is very uncommon. Very few cases have been reported till now. We report a case of such interaction leading to INR more than 10.

Case history

A 52 years old female, resident of Manali, Kullu, Himachal Pradesh, presented with chief complaint of shortness of breath for about one month. She was a known case of rheumatic heart disease for last 20 years and on prophylaxis with injection Penidure LA intermittently from local hospital. Patient was apparently well about one month back when she started having shortness of breath, which was gradual in onset and progressive in nature, initially shortness of breath on walking uphill, but for last 3-4 days even on level walk. History of shortness of breath on lying down, abnormal awareness of heart beat even in character in 6th intercostal space lateral to left mid clavicular line. Grade 3 parasternal heave and s2-p2 were palpable.

On auscultation s1 was soft and variable, s2 p2 was loud and a PSM grade 3 best heard at apex radiating to axilla, an ESM at primary aortic area grade 3 best heard in forward bending position. In respiratory system examination fine inspiratory crepts were present b/l ISA, IAA more on right side.

Rest of the systemic examination was normal.

Initial ECG was s/o Atrial fibrillation with fast ventricular rate and ECG during digoxin toxicity (Figure 1) was s/o slow and regularized ventricular rate. X-ray chest was s/o b/l lower zone infiltrates. Her baseline INR was 1.60. Bedside 2D echocardiography was suggestive of severe MS, severe MR, giant left atrium (Figure 2) compromising right atrium, moderate AR and moderate TR.

Patient was started on Torsemide 20 mg, Spironolactone 50 mg, injection enoxaparine 60mg twice a day, Digoxin at rest for last 3-4 days was present. History of swelling feet, decreased sleep, decreased appetite for last 3 days was present. There was no history of chest pain, sweating, fever, cough, joint pains, loss of consciousness. Her urinary and bowel habits were normal.

In her treatment history she was already on tablet digoxin, metoprolol, warfarin, and injection penidure intermittently. She had no history of contact with tuberculosis, anti tubercular drugs intake, diabetes mellitus, hypertension or joint pains. There was past history of episodes of shortness breath. She was para 3+0, with all uneventful deliveries at home. Her last childbirth was about 25 years back. Her menstrual and personal history was non contributory.

On examination patient was conscious cooperative, well oriented to time, place, and person, and was dyspneic at rest. Her pulse rate was 76 per minute irregularly irregular, heart rate was 104 per minute with pulse deficit of 28 per minute. Her blood pressure in right arm in supine position was 114/78 mm of hg. JVP was raised and b/l pitting pedal edema was present up to knee level.

In cardiovascular system examination, precordium was pulsatile, apex beat was palpable and tapping...
49 per minute. Digoxin toxicity was suspected and ECG was s/o changes of digoxin toxicity. So digoxin was stopped and then serum digoxin levels were sent which were above normal level i.e. 3.76 ng/ml (normal 0.80-2.00). So digoxin toxicity was confirmed. There was no suggestion of non compliance, dispensing errors were ruled out, her renal functions and electrolyte panel was normal. As patient was not having any bleeding manifestations, no specific treatment for coagulopathy was done. The levels of Digoxin and INR returned to normal spontaneously. During hospital stay patient later on developed H1N1 influenza pneumonia. She recovered from pneumonia after treatment with oseltamivir 75 mg. She was planned for mitral valve repair later on and was discharged from hospital.

Discussion

Digoxin a cardiac glycoside, is used in heart failure and supraventricular tachycardia. Elimination t1/2 is about 36-48 hours with normal or near normal renal functions. Structurally digoxin has both lipophilic and hydrophilic groups with 75% bioavailability. About 40% of ingested digoxin is bound to plasma albumin. It is excreted unchanged in urine. Principal tissue reservoir of digoxin is skeletal muscle.

10% of general population harbours enteric bacteria Eubacterium lentum, which inactivates digoxin and may cause resistance to digoxin. As our patient was on amoxycilline and clarithromycin, it might have interacted with digoxin resulting in increased effects of digoxin. As in our patient we were giving spironolactone to the patient, it might have interacted with digoxin by decreasing excretion of digoxin and increasing its blood level.

Warfarin has got nearly complete bioavailability when administered orally. Metabolized principally by CYP2C9. Inactive metabolites are excreted in urine and stool. Its t1/2 is about 40 hours and duration of action is about 2-5 days. INR can rise disproportionately due to decreased metabolism of warfarin due to drugs causing inhibition of CYP2C9. In contrast to digoxin, warfarin is 99% bound to plasma albumin, and it can be displaced by weakly acidic drugs.

Unbound fraction of this drug is pharmacologically active and metabolized by hepatic microsomal enzymes. Common interactions of warfarin with other drugs are due to induction or inhibition of microsomal enzymes or displacement of warfarin from plasma albumin. Some drugs like valproate, loop diuretics may displace warfarin from protein binding site and making more warfarin available for action. If there is increased free warfarin available, it will lead to increased anticoagulant effect.

In this case all other possibilities were ruled out except interaction with digoxin toxicity. As already explained digoxin is 40% plasma albumin bound, in case of digoxin toxicity more of digoxin will bind to plasma albumin and displace warfarin from plasma albumin. So that more pharmacologically active warfarin will be available. That will lead to high INR. Also there was possibility of amoxycilline related alteration in gut flora causing decreased metabolism of both warfarin and digoxin.

A similar case of 66 years old male has been previously reported by Arpandev Bhattacharyya and Manju Bhavnani in British Journal of Cardiology who was a diabetic patient with nephropathy and atrial fibrillation on secondary prophylaxis with warfarin.

This patient presented with coagulopathy secondary to raised digoxin level. Digoxin levels were raised due to diabetic nephropathy leading to decreased excretion of the drug.

Another case reported in Annals of Pharmacotherapy of 72 years lady who was on digoxin and warfarin for chronic atrial fibrillation, was prescribed clarithromycin for H. pylori eradication. she presented with gastrointestinal symptoms, dizziness, visual symptoms 12 days after initiation of clarithromycin.

Laboratory investigations revealed raised digoxin levels and INR. In this case clarithromycin led to inhibition of hepatic microsomal enzymes causing raised levels of warfarin and inhibition of gut flora leading to alteration in digoxin metabolizing gut flora causing further raised digoxin level.

Conclusion

One has to be alert when such pharmacodynamically volatile drugs are prescribed.

References

