

# Digoxin Toxicity presented with Right Bundle Branch Block: A Case report of Drug- Drug Interaction

Patel S.R.<sup>1</sup>, Makwana H.D.<sup>2</sup>, Patel K.P.<sup>3</sup>, Malhotra S.D.<sup>4</sup> Patel P.R.<sup>5</sup>

<sup>1</sup>Dr. Shreya R Patel, <sup>2</sup>nd Year PG Resident, Department of Pharmacology, <sup>2</sup>Dr. Harsha D Makwana, Associate Professor, Department of Emergency Medicine, NHL, MMC, Ahmedabad, <sup>3</sup>Dr. Kamlesh P Patel, Associate Professor, Department of Pharmacology, <sup>4</sup>Dr. Supriya D Malhotra, Professor and Head, Department of Pharmacology, <sup>5</sup>Dr. Pankaj R Patel, Dean, all authors are affiliated with NHL, MMC, Ahmedabad, Gujrat, India

**Address for Correspondence:** Dr Harsha D Makwana, Email: drharsham@gmail.com

## Abstract

Digoxin, one of the digitalis glycosides has specific effects on the myocardium. The effects of Digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. It is the most common drug used in treatment of congestive heart failure and tachy-arrhythmias. It is used in treatment of arrhythmias but when arrhythmias occur in a patient on maintenance dose of Digoxin, its toxicity should be suspected. Here we report a case of Digoxin toxicity with the therapeutic dose confirmed by elevated Serum Digoxin levels. This occurrence could be due to Digoxin itself or this adverse effect could be predisposed by a suspected drug –drug interaction (SDDI) with the concomitant drugs this patient was prescribed.

**Key words:** Digoxin, RBBB, Adverse drug reaction, Therapeutic drug monitoring, SDDI

## Introduction

Digoxin is one of the cardiac glycosides, a closely related group of drugs having common specific effects on the myocardium. The effects of Digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. Intrinsic impairment of conduction in the right leads to prolongation of the QRS interval. With right bundle branch block, the terminal QRS vector is oriented to the right and anteriorly and it also occurs with valvular heart diseases. But it can also have

manifested with Digoxin toxicity[1]. Digoxin being a narrow therapeutic index drug can be influenced by many other drugs which could alter its volume of distribution ( $V_d$ ) and clearance and predispose to toxicity.

Here in we present a case report in which patient developed RBBB subsequent to Digoxin given in therapeutic dose. Despite giving in therapeutic dose Digoxin levels were elevated in this patient. The authors attribute this occurrence to a SDDI with other prescriptions drugs of the patient.

## Case History

A 65 years old female patient was admitted to emergency department with complains of shortness of breath and Gabharamanfor 2 days. It was associated with abdominal pain, tinge of blood in sputum, pedal edema, and decreased frequency of urination. Patient is known case of Rheumatic Heart Disease along with Mitral Regurgitation, Mitral Stenosis and Pulmonary Arterial Hypertension since 40 years. Uneventful mitral valvotomy was done before 40 years. She was taking regular treatment in the form of Tab. Digoxin (Lanoxin) 0.25 mg OD, Tab. Warfarin 2mg OD, Tab. Atenolol 50mg OD, Tab. Furosemide 20mg + Spironolactone 50mg BD and Tab. Diltiazem 60mg BD. She was also on Inj. Penicillin prophylaxis at the time of presentation.

Manuscript received: 5<sup>th</sup> October 2017

Reviewed: 15<sup>th</sup> October 2017

Author Corrected: 24<sup>th</sup> October 2017

Accepted for Publication: 30<sup>th</sup> October 2017

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On examination patient was drowsy but arousable. Her vitals were: Pulse- 70/min & Irregular, BP- 124/80mm Hg, RR- 20/min, and Temperature- Normal, RBS- 133 mg/dl. Her SpO<sub>2</sub> was 76% on room air so oxygen was given initially by high flow mask at 15 litres/min and then O<sub>2</sub> with BiPAP support. On auscultation fine basal crepitations were present, CVS – Diastolic Murmur at Apex and Systolic Murmur at Pulmonary area present, S2 loud.

All her routine drugs were withheld. Cardiology referral was done. On blood examination all investigations Serum Digoxin level was 2.31 ng/ml (normal 0.8-1.4) and S.K<sup>+</sup> was 6.1 mEq/l (normal 3.5-5.1mEq/l) (Table 1). A diagnosis of Digoxin toxicity was made by the treating physician.

**Table-1: Investigations.**

CBC Hb.-11.2mg/dl WBC- 7900 /cmm Platelets- 67,500	S. Creatinine- 0.9mg/dl S. K <sup>+</sup> - 6.1mEq/l (High) (subsequent-5.6, 4.2) S.Acetone – Absent Troponin-I- 0.018 ng/ml (normal) Other S. electrolytes were normal <b>S. Digoxin level -2.31ng/ml (normal- up to 1.4 ng/ml)</b>
2D Echocardiography Severe mitral stenosis-MVA= 0.8 cm <sup>2</sup> , 20/11mm Hg Moderate mitral regurgitation Type-2/3 atrial regurgitation Severe tricuspid regurgitation. ECG Atrial Bradycardia with Varying block and right bundle branch block (RBBB).	USG Abdomen: Left Kidney- small in size (98.30 mm) Gall Bladder- Thickening (4mm) present IVC Diameter- 8mm with dilated hepatic vein suggesting congestive changes

On 2<sup>nd</sup> day of admission patient was Conscious, Oriented and better. Her Temp.-Normal, Pulse- 80/min Irregular, BP- 128/80 mm Hg and SpO<sub>2</sub>-80% on room air and. On auscultation same findings as previous one so BiPAP support with oxygen continued.

Maintenance treatment continued with Inj. Furosemide 20 mg IV BD, K<sup>+</sup> binding sachet TDS, Inj. Pantoprazole 40mg IV BD, Inj. Ondansetron 4mg IV BD, Inj. Vit.K 1unit IV OD, Tab. Diltiazem 60mg BD, Nebulise. Duolin TDS., Inj. Amikacin 1gm 8hrly, Inj. Moxicillin+ Clavulanic Acid 1gm 8hrly and BiPAP support.

Progress from 3<sup>rd</sup> day to 7<sup>th</sup> day  
S. K<sup>+</sup> level- decreased (5.6 mEq/l)

SpO<sub>2</sub> improved (94% on room air) so BiPAP and oxygen support withdrawn on 5<sup>th</sup> and 7<sup>th</sup> day subsequently Tab. Diltiazem 60mg BD and Inj. Heparin 5000 IU SC BD started on 3<sup>rd</sup> day. All other reports were normal. Subsequently patient improving clinically.

This case was considered as Digoxin toxicity because of Drug-Drug Interaction. The case was reported via Vigiflow to the National coordinating center for ADR monitoring with reference ID No. is 2017-13723. According to WHO-UMC Causality Assessment Criteria this Adverse Drug Reaction falls in to probable / Likely causality.

**Discussion**

Digoxin is the one of the commonly prescribed drug for treatment of Congestive Heart Failure (CHF). In CHF it increases contractility by inhibiting Na<sup>+</sup>/K<sup>+</sup> ATPase pump in myocardial

cells which subsequently promotes the Ca<sup>2+</sup> influx via Na<sup>+</sup>- Ca<sup>2+</sup> exchange pump. Because of its Pharmacokinetics properties and a narrow therapeutic index, it frequently leads to toxicity.

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Now days the severity and incidence of Digoxin toxicity have reduced because alternative drugs are available. There is also increased understanding related to pharmacokinetics, serum Digoxin level monitoring facilities available, and awareness towards identification of important interactions between Digoxin and other commonly administered drugs. To identify Digoxin toxicity, an important consideration is the differential diagnosis of arrhythmias, neurologic or gastrointestinal symptoms.

Among the more common electrophysiological manifestations of Digoxin toxicity are ectopic beats originating from the AV junction or ventricle, first-degree AV block, abnormally slow ventricular rate response to atrial fibrillation, or an accelerated AV junctional pace-maker[2]. But in our case manifestation was arrhythmias with Right Bundle Branch Block. (RBBB) which is not commonly seen. Gill D et al. also presented a case of digoxin toxicity with RBBB[1].

There are many factors which lead to Digoxin toxicity such as age, comorbid condition, and electrical cardioversion, concomitant administration of beta blockers, calcium channel blockers or antibiotics drugs. In our case patient presented with Digoxin toxicity despite being prescribed normal therapeutic dose. It could be possibly due to concomitant drugs prescribed to the patient.

Diltiazem decrease Digoxin clearance, likely by inhibiting P-glycoprotein which is the major route of Digoxin elimination. Because of this pharmacokinetic property new steady-state Digoxin concentrations are approached after 4-5  $t_{1/2}$  (i.e. in about a week).[2]

Diltiazem also undergoes extensive firstpass hepatic metabolism. Diltiazem and Digoxin both drugs have metabolites that exert  $Ca^{2+}$  channel-blocking actions. In clinical practice, adverse effects during therapy with Diltiazem are determined largely by underlying heart disease and concomitant therapy.

And plasma concentrations of these agents are also not measured routinely. Both drugs can increase serum Digoxin concentration. Diltiazem also have additive effect in AV conduction so it can interact with Digoxin pharmacodynamically also. [2]

Beta blockers may also increase the risk of heart block and bradycardia with digoxin. Carvedilol has been reported to increase plasma concentrations of digoxin. It interacts with the clearance of Digoxin and leads to toxicity. Talinolol an adrenergic beta antagonist; increase in digoxin bioavailability but not with Atenolol which can also cause Bradycardia and toxicity[2].

With Spironolactone also Digoxin toxicity occurs and it is not established type of DDI. Spironolactone increases the plasma concentration of Digoxin by decreasing the volume of distribution and plasma renal clearances. Near maximal capacity for the tubular secretion of Digoxin was found when normal Digoxin dosage was used.

It is suggested that unless spironolactone decreases the myocardial sensitivity for Digoxin, the loading dose as well as the maintenance dose of Digoxin should be reduced during treatment with spironolactone[3].

Use of diuretics with Digoxin increased the risk of hospitalization for Digoxin intoxication, and the risk was higher for combinations of diuretic classes. Especially the combination of loop diuretics, thiazides and potassium-sparing diuretics in conjunction with Digoxin carried the highest risk. Mechanism for this is Digoxin reversibly inhibits sodium-potassium ATPase (Na, K-ATPase or the Na, K pump) and competes with to binding to the Na, K pump.

So the inhibition of the Na, K pump by digoxin is facilitated by the reduced serum potassium concentration by diuretics. And hypokalemia can also cause Arrhythmias. But in our case patient did not have hypokalemia so it means diuretics was not culprit for toxicity[4].

### Conclusion

This case report was considered as Digoxin toxicity with routine therapeutic dose, because of Drug-Drug Interaction as patient was on drugs for her medical condition which included Diltiazem and Atenolol. Both the drugs retarded the clearance of digoxin leading to its high levels.

**Take Home message:** While treating such patients, all the factors leading to drug toxicity even at

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therapeutic range should be kept in our mind and managed accordingly. One should be watchful for the drug-drug interaction and in vulnerable cases plasma level of the drug should be done as soon as suspected or any sign or symptoms related to toxicity.

**Acknowledgement:**We are thankful to Dr. S. T. Malhan, The Medical Superintendent of our hospital and for allowing us to publish this case report.

**What this study add to existing knowledge?:** Digoxin is one of the oldest drug to treat heart failure. It's a known fact that Digoxin could be responsible for any kind of Arrhythmias. Digoxin being a drug for narrow therapeutic index can have its plasma levels increased by co-administered drugs which can affect metabolism of digoxin. Hence the authors want to bring to light this unexpected SDDI of Digoxin with Diltiazem and Atenolol.

**Contribution of Authors:**Concept was given by Dr. HarshaMakwana, Dr. Shreya Patel, Dr. Supriya Malhotra, Dr. Kamlesh Patel. Literature search and manuscript preparation by Dr. Shreya

Patel and Dr. Harsha Makwana. Editing and Review of manuscript by Dr. Kamlesh Patel and Dr. Supriya Malhotra and Dr. Pankaj Patel.

**Funding:** Nil, **Conflict of interest:** None

**Permission of IRB:** Yes

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### How to cite this article?

Patel S.R, Makwana H.D, Patel K.P, Malhotra S.D, Patel P.R. Digoxin Toxicity presented with Right Bundle Branch Block: A Case report of Drug- Drug Interaction. *Int J Med Res Rev* 2017;5(10):921-924. doi:10.17511/ijmrr. 2017.i10.08