

## A Case Report on Chronic Digoxin Toxicity

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### Abstract:

Digitalis glycosides are among the oldest drugs used in cardiology. Nowadays, due to the limited indications for their use (advanced heart failure, usually concomitant with atrial fibrillation), cases of toxicity induced by this class of drugs are rarely observed. Digoxin produces a positive inotropic and bathmotropic effect on the heart, but has a negative chronotropic and dromotropic effect. Cardiac glycosides have a narrow therapeutic window, so digitalis treatment can easily lead to symptoms of overdose. In patients taking digoxin, the drug therapeutic level should be maintained at 1-2 ng/ml; the toxic effects occur at concentrations > 2.8 ng/ml and are mainly related to disturbances of cardiac function and of the circulatory system, as well as gastrointestinal symptoms and CNS disturbances. Here, a 65-years-old patient who was hospitalized following chronic ingestion with acute renal

impairment. In spite of rapidly applied gastric irrigation and administration of activated charcoal, the drug level in the patient's blood was estimated at 8.5 ng/ml. During her stay on the ward, typical symptoms of severe toxicity were observed: from gastric symptoms (severe nausea, vomiting) to conduction disturbances. Type I, moitz type 1 and 2 AV blocks were detected, as well as some supraventricular extrasystoles. These conduction disorders required the use of temporary endocardial pacing. Due to the unavailability of specific antidotes (antidigitalis antibodies) and lack of efficient methods of extracorporeal elimination of the drug, symptomatic treatment comprising the correction of electrolyte disturbances and heart rate control remains the most effective.

**Keywords:** Poisoning, digitalis. Atrioventricular block. Antidigoxin antibodies.

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### Introduction:

Digoxin is a centuries old drug which continues to be used in congestive heart failure and cardiac rhythm disorders particularly atrial fibrillation. But indications are increasingly restricted day by day. A therapeutic concentration of digoxin is reported as 0.8-2.0 ng/mL<sup>1-2</sup>. Because of its narrow therapeutic index, patients on digoxin are at risk for toxicity. Digoxin-specific antibody fragments serve as a therapeutic option in patients with digoxin toxicity; however, the indications for digoxin-specific antibody fragments are inconsistent. In a review of the literature, Lloyd et al., in

2014, reported the efficacy of digoxin-specific antibodies as ranging from 50%-90%<sup>3</sup>. Here discussion on a case of a symptomatic elevated digoxin level of 8.5 ng/mL secondary to a dosing error and AKI due to urosepsis, who was managed without digoxin-specific antibody fragments as well as a brief information about digoxin toxicity.

### Case report:

A 65-year-old diabetic, normotensive woman presented to Evercare hospital dhaka emergency department with

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a chief complaint of loose motion and vomiting for 3 days. She was also experiencing dizziness, drowsiness, fatigability and nausea for two weeks. She has a history of myocardial infarction 3 months back and treated with thrombolytic. Coronary angiogram was done which revealed left main and triple vessel disease and CABG was done in the same setting. Hospitalization two months prior to current presentation, patient was treated for heart failure with paroxysmal atrial fibrillation. Her medication list revealed that she had been discharged on digoxin. Her past medical history was pertinent for heart failure with a reduced ejection fraction with LVEF 30%. Due to nausea, she discontinued digoxin which was advised by physician.

She presented with mild disorientation. Initial vitals included blood pressure 80/60 mmHg, heart rate 48 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation of 94% on 3 L/min of oxygen via a nasal cannula. EKG showed 2:1 atrioventricular block

with ventricular rate of 48 bpm (Figure 1). Lab results included potassium 3.5 mmol/L (normal range 3.5-5.0 - mmol/L), creatinine 1.5 mg/dL (normal range 0.7-1.3 mg/dL), troponin 0.03 ng/mL (normal <0.03 ng/mL), and digoxin 8.7 ng/mL (therapeutic window 0.8-2.0 ng/mL). After a discussion with the family and patient, the decision was made to treat the patient with supportive care in the emergency department (ED). After initial management, she was admitted into CCU and Inj. Noradrenalin was started for hypotension. Inj. Atropine failed to revert AVB. With conservative management her condition stabilized. Oral potassium was given with the target of level of > 4 mmol/L. Her digoxin concentration trended down at the expected rate She remained asymptomatic during her hospital stay with normalization of ECG (Figure 2). It was recognized that raised blood digoxin level was due to acute renal impairment. She was discharged against medical advice on hospital Day 4 due to financial constraint (Digoxin level 3.2ng/mL).

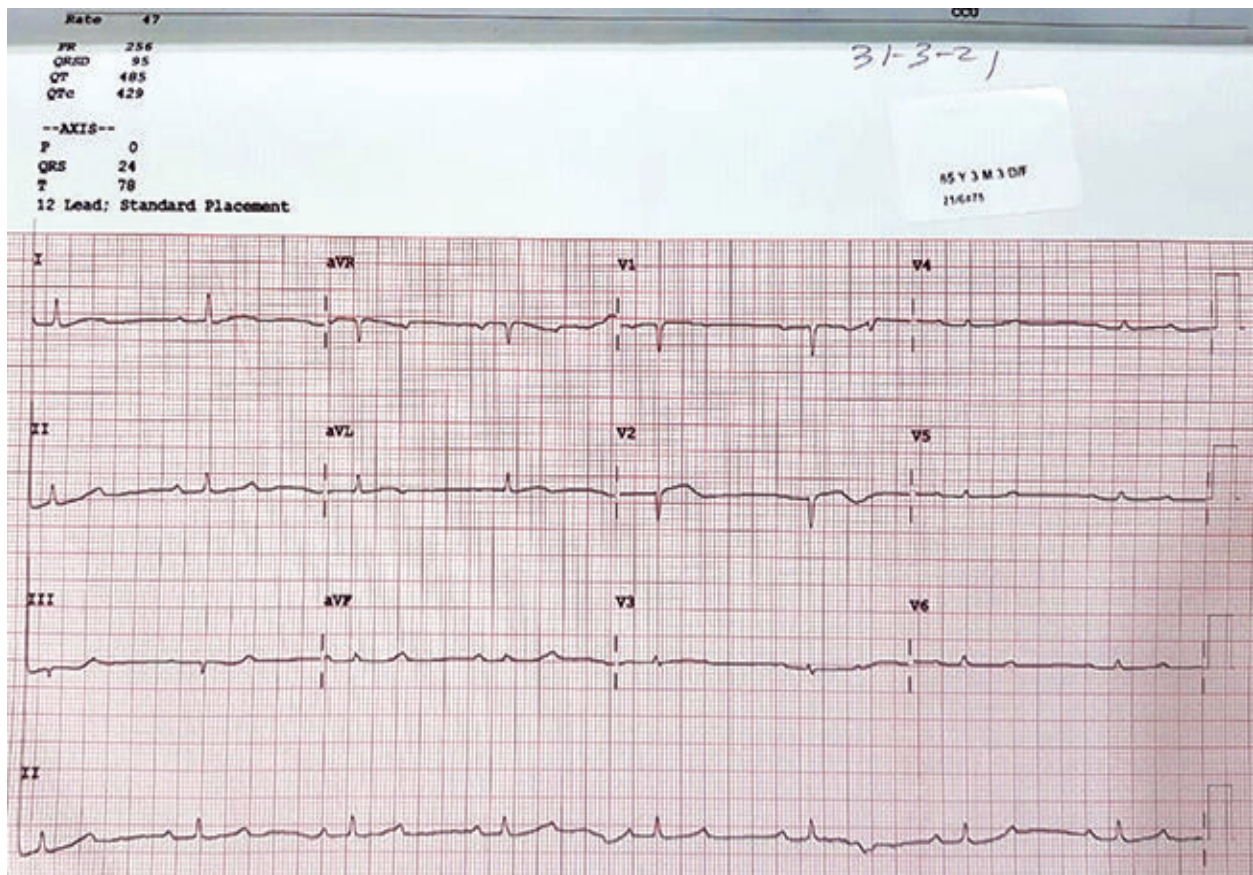


Fig-1: 12 lead ECG showing 2:1 AV block.



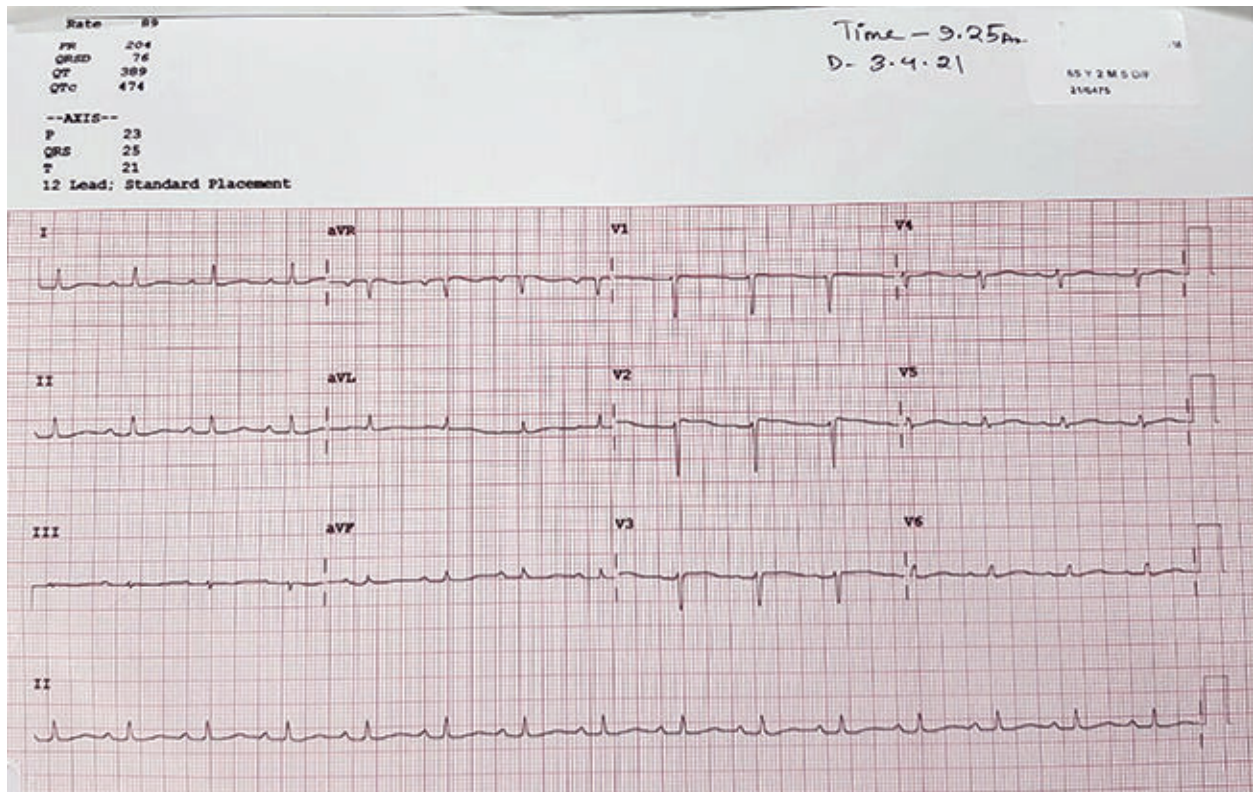


Fig.-2: 12 lead ECG showing normal sinus rhythm.

**Discussion:**

Digoxin is one of the common cardiac drug used in past and present. Digitalis toxicity, particularly in persons under long-term digoxin therapy, is a reason for repeated visits to hospital. Acute poisoning is rare but may occur as a result of attempted suicide or the intake of plants

that contain cardiac glycosides. This glycosides found in plants like *Digitalis purpurea* (foxglove) and *Digitalis lanata* (woolly foxglove). Below in table I pharmacologic profile was given<sup>4</sup>.

In acute poisoning the patient may present initially asymptomatic for 1-2 hours before symptoms such as

**Table-I**

Bioavailability	65-80%
Protein binding	20-25%
Metabolism	Liver (10-20%)
Elimination half-life	35-45 hours
	3.5 - 5 days (if renal failure)
Excretion	Kidney (75-80%)
Solubility	water
Mechanism of action	Inhibit the sodium-potassium-ATPase
Effect begins	30-90 minutes
Peak effect	4-6 hours
Serum threshold Dose	0.8-2.0 ng/mL.
Volume distribution	
• Adult	4-7 l/kg
• Child	16 l/kg
Lowest Reported Toxic Dose-	
• Adult	7500 mg
• Child	0.05 mg/Kg and 4 mg

nausea, vomiting, diarrhea and abdominal pain appear. Then followed by lethargy, confusion and weakness, regardless of the hemodynamic situation. Chronic toxicity produces less specific initial symptoms, such as loss of interest in daily life activities, anorexia, nausea, vomiting, diarrhea, abdominal pain, weight loss, delirium, confusion, drowsiness, headache, hallucinations, visual disturbance (chromatopsia, particularly xanthopsia), instability, syncope or fainting due to low cardiac output associated with altered heart rate<sup>5</sup>. One third of patients who die do so because of bradyarrhythmia and two thirds because of ventricular arrhythmia, but bradycardia that is unresponsive to atropine may be premonitory of ventricular fibrillation<sup>6</sup>.

**Table-II**  
*Arrhythmias found in digitalis poisoning*

Bradyarrhythmia	Tachyarrhythmia
Sinus bradycardia	Atrial tachyarrhythmia
Sinoatrial block	Junctional tachycardia
Mobitz type II 2nd degree AVB	Ventricular extrasystole
Atrioventricular dissociation	Bigeminy
Slow Atrial fibrillation	Ventricular tachycardia
Atrial flutter with AVB	Ventricular fibrillation

Diagnosis is done by history, clinical symptom, compatible ECG findings and serum digoxin level. Other laboratory tests include kidney function test, liver function test, serum electrolyte calcium, ABG and serum magnesium.

Specific treatment for digoxin toxicity is administration of digoxin-specific Fab fragments (antibodies) who are hyperkalemic or have Life-threatening situations (table III). For acute toxicity with an unknown digoxin concentration and unknown amount ingested, 10 vials can be empirically administered for adults, or 5 vials for children. For chronic toxicity, these doses will likely overestimate the amount of digoxin immune Fab fragment needed. One vial of digoxin immune fragments binds to 0.5 mg of digoxin. If the digoxin concentration is known, and the patient has ingested digoxin, the following formula can be used:

Number of vials = (serum digoxin concentration) x (patient weight in kilograms)/100<sup>7</sup>.

For the supportive management the first priority is ensuring the patient has an adequate airway and breathing. An intravenous line should be established, with supplemental oxygen supplied if necessary and intravenous fluid therapy with control of central venous pressure (CVP). In chronic toxicity, digoxin and any other antiarrhythmic should be discontinued.

**Table-III**  
*Life-threatening situations where anti-digoxin antibodies was indicated<sup>8</sup>*

Bradycardia with HR < 40 bpm and no response to atropine.	PVC with risk of VT or VF
Ventricular tachycardia. Asystole.	Ventricular fibrillation. Digoxin plasma levels > 6 ng / mL (> 6 hour post-ingestion).
Cardiogenic shock.	Potassium > 5 mEq/L in acute intoxication.

In acute poisoning (<6h) gastrointestinal decontamination with activated carbon to prevent absorption should be considered. Hypokalemia is treated with supplementary potassium until it is > 4 mEq/L. Hyperkalemia (K<sup>+</sup> > 5 mEq/L) should be corrected with extreme caution using insulin-glucose, bicarbonate or exchange resins and Hyperkalemia may also be corrected with calcium salts, but in digitalis toxicity they may induce asystole or malignant arrhythmias so are not recommended. Neither is it advisable to treat hyperkalemia with beta-adrenergic because of their arrhythmogenic potential. Hyperkalemia in the presence of renal failure is an indication for hemodialysis<sup>9</sup>.

Hypomagnesemia is common in chronic poisoning due to the frequent use of diuretics in these patients. In theory, magnesium reduces myocardial irritability and improves conduction; it is indicated if sustained ventricular arrhythmia is present, but this benefit has not been confirmed in controlled studies. Magnesium is contraindicated in the presence of renal failure, bradyarrhythmia or AVB<sup>11</sup>. The correction of hypocalcemia is controversial and uncertainty about its cardiac effects; in cases of digitalis toxicity, calcium salts should not be administered<sup>12</sup>.

In hypotension, plasma volume should be increased within limits<sup>1</sup> and correction of hypoxemia if present. Dopamine or dobutamine are potentially arrhythmogenic and should be avoided. In refractory cases, noradrenaline is the drug of choice. Hypertension is rare and if needed then one should use drugs with a short half-life.

Management of arrhythmias is shown in figure 3. The use of pacemakers has very limited indications, since they do not guarantee control of rhythm disorders, and intra-cardiac placement is nowadays totally contraindicated, especially in acute poisoning, since they can induce malignant arrhythmias<sup>13</sup>. But some authors have obtained good results in cases of chronic poisoning, and recommend temporary pacemakers in patients with

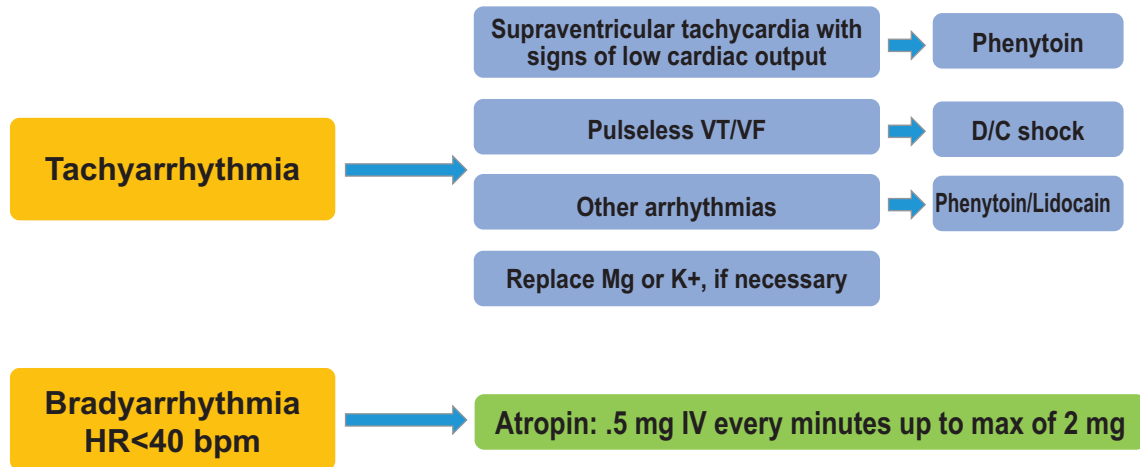


Fig.-3: Management of arrhythmias in digoxin toxicity<sup>10</sup>.

advanced AVB or symptomatic bradycardia, programmed at low frequencies (55-60 beats/min) to minimize their arrhythmogenic effect<sup>14</sup>.

Direct cardioversion to reverse supraventricular tachyarrhythmia has been associated with fatal ventricular arrhythmia and should not be used. However, cardioversion or defibrillation is indicated in situations of unstable or pulseless ventricular tachycardia and ventricular fibrillation. In these situations it is recommended to start with low energy (10-25 J) and pre-treat, if possible, with lidocaine or amiodarone<sup>15</sup>.

For renal and extra-renal clearance, diuresis and hemodialysis or hemoperfusion are ineffective at significant extraction of digoxin, mainly due to its extensive volume of distribution. Once over the period of major risk period, with no signs, symptoms and ECG changes related to digitalis poisoning and with digoxin concentrations < 2 ng/mL, the patient can be discharged.

#### Conclusion:

Digitalis toxicity is serious and, from the beginning, the patient must be monitored continuously while risks are evaluated, treatment administered and until risk of death is considered improbable. Digoxin-binding antibody is the only drug which can reverse the effect of digoxin toxicity. In perspective of Bangladesh, unfortunately this antidote is not easily available medicine. Due to the unavailability of specific antidotes (antidigitalis antibodies) and lack of efficient methods of extracorporeal elimination of the drug, symptomatic treatment comprising the correction of electrolyte disturbances and heart rate control remains the most effective.

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