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# Digoxin Toxicity- Uses and its managements

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**ABSTRACT:**
We aim to review on recent development on digoxin toxicity focusing on digoxin, mechanism underlying the process, causes of digoxin toxicity, uses and its management of digoxin toxicity in patients, and the treatments. Digoxin belongs to a group of medications known as cardiac glycosides and categorized in drug substance. Digoxin discovered in 1785 obtained from foxglove leaves but with the adivance available to prove that the uses of digoxin have been taken since 2000 years ago. An ample amount of water required for the patients who intake the digoxin. Due to loss of potassium level, risk of digoxin toxicity increased; therefore, in order to attempt precise treatment,, regular monitoring is required for those who shows little or more symptoms of digoxin toxicity. With all safe measures, digoxin treatment can be safe, effective, and cost-effective. Activated charcoal can be used for the treatment resulting lowering down the effect of digoxin toxicity. Specific digoxin antibody-fragments can be used in the treatment of life-threatening digoxin toxicity. DigiFab and DigiBind are available which initiated from ovine, gathered and cleaned from sheep, immunized with human albumin and combined with digoxin. These digoxin molecules combine with antibody-fragments to prevent them from combining with their receptors.

## I. INTRODUCTION

Digoxin is composed of a sugar (glycone) and cardenolide (aglycone) moieties; its molecular formula is C41H64O14, and its molecular weight is 780.95 Da[9]. Digoxin is sold under the brand name Lanoxin and is considered one of the top poisons in the world due to: i) Wide availability, and, ii) Narrow therapeutic window. Cardiac glycosides are atypical to have a constricted therapeutic range, which varies from individual to individual. In pursuance of this it may be not surprising that toxicity being a common occurrence have been reported in 30 to 35 % of the patient. Digoxin is commonly used for the treatment of atrial fibrillation, especially with co-existing congestive heart failure[1]. For heart failure, the recommended range for the serum digoxin concentration has been reduced over the past decade from 0.8–2.0 nanogram/mL to 0.5–0.9 nanogram/mL[2]. Cardiac glycosides which include digoxin slow down the sodium-potassium-ATPase, that results hike in intracellular sodium and extracellular potassium that eventually results in increased intracellular calcium and inotropy[8]. The excessive intracellular calcium can result in delayed after-depolarizations, which may result in premature contractions and dysrhythmias. Many mechanisms cause this problem. Digoxin reported to be taken mainly by the kidneys, and therefore, any impairment function may lead to higher than expected plasma concentrations. Almost 30% of digoxin is plasma protein bound. Several other clinical conditions such as hypothyroidism, chronic lung disease and cardiac amyloid are associated with an abnormally high myocardial sensitivity to digoxin. Despite all of this, however, there is often still no clear relationship between these factors and manifest toxicity. Digoxin has been proven beneficial for symptomatic control in sinus rhythm in patients with mild to moderate heart failure. In the PROVED trial, treatment of heart failure is another historical use. Symptoms that improved secondary to digoxin therapy included ejection fraction, heart rate, and exercise capacity.

Digoxin toxicity can induce literally every arrhythmia except for rapidly conducted atrial arrhythmias (atrial fibrillation and atrial flutter). The classic arrhythmias seen during digoxin toxicity include atrial tachycardia with a 2:1 conduction, bidirectional ventricular tachycardia and atrial fibrillation with a slow ventricular response. Cardiac arrest and death can occur from ventricular fibrillation, ventricular tachycardia and severe bradyarrhythmias. For heart failure, the recommended range for the serum digoxin concentration has been reduced over the past decade from 0.8–2.0 nanogram/mL to 0.5–0.9 nanogram/mL. This is because of evidence of better outcomes at lower concentrations. Whether this

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range should also apply to patients with atrial fibrillation without heart failure is unknown.

## II. CURRENT STATUS

There was a decline noted in the progress of Digoxin since 1990[3]. Digitalis use was first described in 1785 and was derived from the foxglove plant. Poisoning with digitalis can occur with acute over-ingestion of medication or as chronic toxicity most commonly due to decreased renal clearance. Some metabolic disturbances such as hypokalemia and hypercalcemia can make one more prone to toxicity as well as some drug interactions. Digoxin use has declined since the 1990s. While the overall incidence of toxicity per population has also declined, the incidence per treated patient may have remained unchanged. The Australian Institute of Health and Welfare records cardiac glycoside toxicity as the diagnosis on hospital discharge in 280, 233 and 139 patients in 1993–94, 2003–04 and 2011–12 respectively[4]. Chronic toxicity is far more common than acute intoxication.

## III. MODE OF ACTION

The mode of action or mechanism is very important as it holds the therapeutic indications of digoxin. This mechanism is largely depends on two dependent variables, first is cardiac rate and rhythm, and second is the force of cardiac contraction. The slowing of cardiac rate and rhythm are attributed to digoxin's impact on the central nervous system that leads to increased vagal activity resulting in slowed conduction in the atrioventricular (AV) node. The increase in the force of cardiac contraction is attributed to digoxin's binding to the Na+/K+-ATPase pump. By binding to the K+-binding site of the pump, digoxin leads to inhibition of the pump. The consequent rise in Na+ concentration causes slowing of Ca+2 efflux via the Na+/Ca+2 exchanger and a relative increase in intracellular Ca+2. The extra Ca+2 increases the action potential of cardiac cells with more activation of the contractile machinery. Based on the latest data, it has been noticed that the risk of using digoxin on atrial fibrillation is more due to thrombogenesis which increase intracellular Ca+.

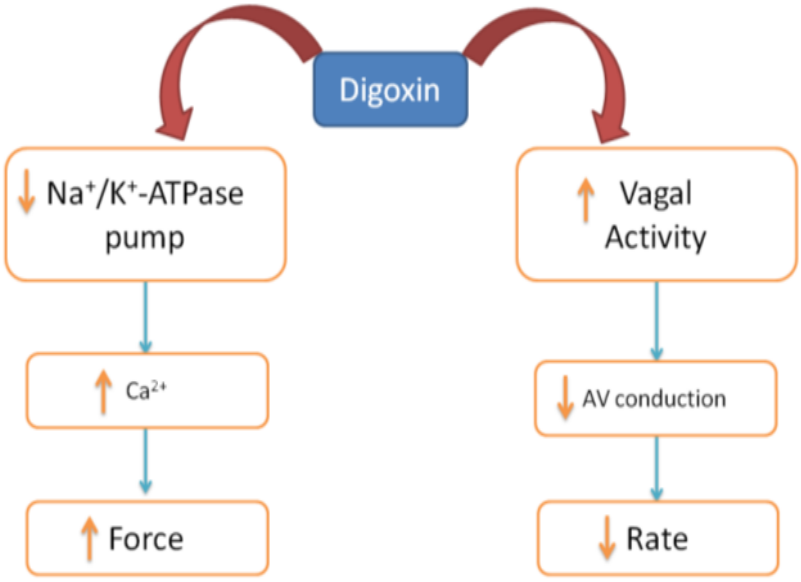


**Fig 2:** Mechanisms of action of digoxin.

Many researchers have proved that, digoxin therapy improved symptoms, including exercise capacity, heart rate and ejection fraction. In the radiance study, digoxin withdrawal resulted in clinical deterioration, such as reductions in systolic function and worsening of exercise tolerance. The most recent practice guidelines for the treatment of heart failure recommend considering the addition of digoxin in patients with persistent symptoms during therapy with an angiotensin-converting enzyme inhibitor (ACEI), a β blocker, and diuretics. Furthermore, digoxin may be added to the initial regimen in patients with severe symptoms who have not yet responded symptomatically during treatment with diuretics, an ACEI, or a β blocker.

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## IV. USES AND ITS MANAGEMENTS

Digoxin increases intracellular calcium in myocardial cells indirectly, by inhibiting the sodium–potassium pump in the cell membrane. Increased intracellular calcium increases cardiac contractility, but also the risk of tachyarrhythmias[5]. Inhibition of this pump causes the hyperkalaemia commonly seen in toxicity. Digoxin also causes an increase in vagal activity, reducing activity in the sinus node and prolonging conduction in the atrioventricular node. After a dose of digoxin, distribution to the tissues takes several hours. This means that the serum digoxin concentration is inaccurate unless taken at least six hours after the last dose. Only a post-distribution measurement reflects the severity of intoxication and this is the measurement that can help when calculating the dose of digoxin-specific antibody[6]. This applies in both acute and chronic poisoning.

The elimination of digoxin is mainly by renal clearance and is prolonged in patients with renal impairment. Transport by P-glycoprotein also contributes to elimination.8 Consequently, a higher serum digoxin concentration for a given dose occurs in patients with renal impairment, lower body weight and in those taking amiodarone, verapamil, macrolides, azole antifungals and cyclosporin, which inhibit P-glycoprotein transport. Although the serum digoxin concentration does predict the likelihood of toxicity, several conditions increase sensitivity to digoxin. They at least partly account for patients who develop toxicity when their serum digoxin concentration is within the therapeutic range. These conditions include hypokalaemia, hypomagnesaemia, hypercalcaemia, myocardial ischaemia, hypoxaemia and acid–base disturbances.

There are no evidence-based guidelines for the management of mild to moderate toxicity so there is a wide variation in treatment[7]. Severe toxicity requires hospital admission and consideration of the need for digoxin-specific antibody fragments. Although digoxin-specific antibody fragments are safe and effective, randomised trials have not been performed. The antibody fragments form complexes with the digoxin molecules. These complexes are then excreted in the urine.

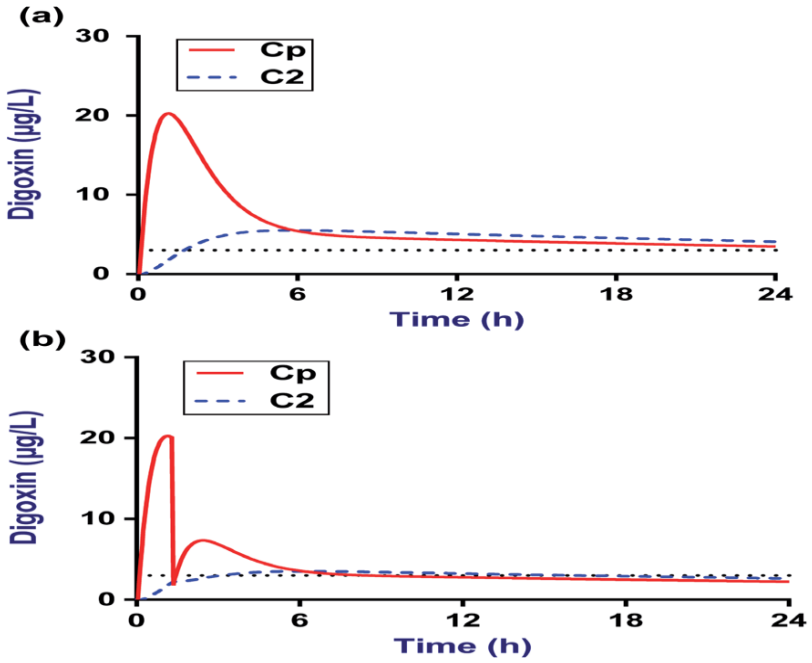


**Fig. 2.** A simulated graph of free digoxin concentrations in the centraland peripheral compartment following an overdose of digoxin 3.5 mg(a) and after treatment with digoxin-Fab 80 mg (b) administered2 h later. If the calculation of digoxin-Fab dose is based on the peak concentration in the distribution phase, then it will be estimated to be800 mg. In this simulated model, digoxin-Fab 40 or 80 mg given duringthe distribution phase would have brought the digoxin concentrationdown signifi cantly by 6 h. A two-compartment model has been used with the following parameters: *F* _ 0.8, Ka _ 1, K21 _ 0.12/h, K12 _ 0.76/h, K10 _ 0.15/h, Vc _ 55 L, Cl _ 7.5 L/h. 56 The dotted line is at 3 µ g/L. Cp _ central compartment, C2 **Chan et al ., 2014).**

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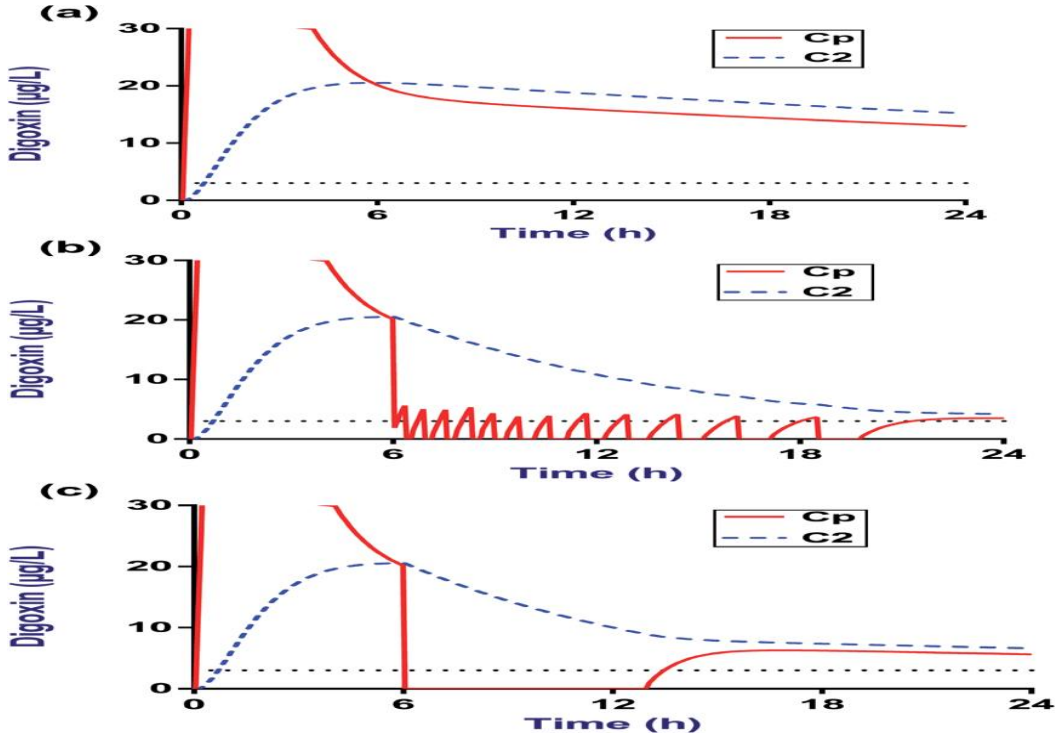


**Fig. 3.** A simulation of free digoxin concentrations in the centraland peripheral compartment of a patient who had taken an acute overdose of digoxin 13 mg (a). (b) The outcome of giving repeated small bolus doses of digoxin-Fab that are titrated against clinical response (with toxicity appearing with concentrations of _ 3 µ g/L). (c) Treatment with a large bolus dose of digoxin-Fab calculated to half neutralise the digoxin load (based on both the ingested dose and the 6 h concentration). There is a late rebound at _ 12 h with a peak free digoxin concentration subsequently of over 6 µ g/L. A two-compartment model has been used with the following parameters: *F* _ 0.8, Ka _ 1, K21 _ 0.12/h, K12 _ 0.76/h, K10 _ 0.15/h, Vc _ 55 L, Cl _ 7.5 L/h. 56 The dotted line is at 3 µ g/L. Cp _ central compartment

The decision to treat a cardiac glycoside-poisoned patient should be supported the presence of hyperkalemia or life-threatening dysrhythmias. For acute toxicity with an unknown digoxin concentration and unknown amount ingested, vials will be empirically administered for adults, or 5 vials for kids. For chronic toxicity, these doses will likely over-estimate the quantity of digoxin immune Fab fragment needed. One vial of digoxin immune fragments binds to 0.5 mg of digoxin. If the digoxin concentration is understood, and therefore the patient has ingested digoxin, the subsequent formula will be used: Number of vials = (serum digoxin concentration) x (patient weight in kilograms) / 100. The patient's weight should be in kilograms, and therefore the digoxin concentration should be in ng/mL. In cases of chronic toxicity without overt hemodynamic instability, one could consider a "partial reversal" during which 1/2 the calculated reversal dosage is run. For an acute ingestion, if the number of digoxin is thought, the number of vials to be administered = (amount of digoxin ingested in mg) / (0.5).

## V. CONCLUSIONS

Digoxin toxicity has gone down with time, which results of a low use and a reduced recommended therapeutic range. This may only happens when the serum concentration is within the optimum range. The presenting features are usually non-specific, the diagnosis can be difficult. In case of life-threatening arrhythmia, these specific antibodies can be used. The amount of these antibodies can be calculated on the basis of the knowledge of the serum to be taken. Further research is needed into optimal dosing protocols and whether digoxin-specific antibody fragments can be cost-effectively used for non-life-threatening toxicity

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