



## DIGOXIN TOXICITY: A REVIEW

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### ABSTRACT

Cardiac glycosides are the important causes poisoning due to widespread clinical uses and presence in natural resource. The digoxin toxicity is common problem in elderly and most commonly seen due to common use of digoxin and because of narrow therapeutic index, therefore most of the physicians are well awareness of classical dose or concentrated related sign and symptom of toxicity. The most common clinical feature of digoxin toxicity is gastrointestinal symptom like nausea, vomiting, abdominal pain and cardiac manifestation included bradycardia, heart block, Supraventricular arrhythmia and ventricular arrhythmia. The incidence of digoxin toxicity has been declines nowadays for a variety of reason including new therapeutic range and development of more effective drug therapy for heart failure and more accurate dose methods. Most case of digoxin toxicity is caused by inappropriately high dose, which are usually prescribed in the setting of renal dysfunctions. Advanced aged, male gender, initial Hyperkalemia, underlying heart disease and advanced AV block at the time of admission are poor prognostic factors. A wide range of treatment have been used, most common are multiple dose activated charcoal, atropine, temporary pacing, electrical cardioversion and anti-Digoxin Fab. Digoxin specific Fab therapy may result in dramatic recovery from digoxin intoxication but it should be administered early and in adequate dose. In modern computerized prescribing system, such as direct physician order, it is possible to decrease the incidence of digoxin toxicity. Death most commonly occurs due to ventricular fibrillation and tachycardia.

**Keywords:** cardiac Glycoside, Digoxin Toxicity, Arrhythmia, Activated charcoal, Digoxin Antibody, Anti Digoxin Fab.

## INTRODUCTION

Digoxin is a cardiac glycoside having cardiac inotropic property, which increase myocardial contractility and output in hypodynamic heart without increase in oxygen consumption. Digoxin slow AV conduction and prolong the refractory period in AV node so help in control the ventricular rate in atrial fibrillation and interrupt re-entry tachycardia involving AV nodes. Digoxin also causes shorten the refractory period and enhances excitability and conduction in other part of the heart including accessory conduction pathways, so it may increase atrial and ventricular ectopic activity and can lead to complex atrial or ventricular tachyarrhythmia. Digoxin causes a dose dependent increase in force of contraction of heart- positive inotropic action, especially seen in failing heart and decrease the heart rate by vagal and extravagal actions. Cardiac glycosides found in several plants and in toad skin (Bufotoxin). Digitalis lanata is the source of Digoxin, the only one glycoside that is currently in use. Digoxin is a cumulative drug when maintenance dose is given from begin, steady state level and full therapeutic effect are attained after seven days. Poisoning due to cardiac glycoside is a worldwide phenomenon. This reflects the long standing and widespread therapeutic use of digitalis glycosides particularly Digoxin. Digoxin poisoning may follow intercurrent illness or prescribing or dispensing illness and accidental or intentional poisoning.

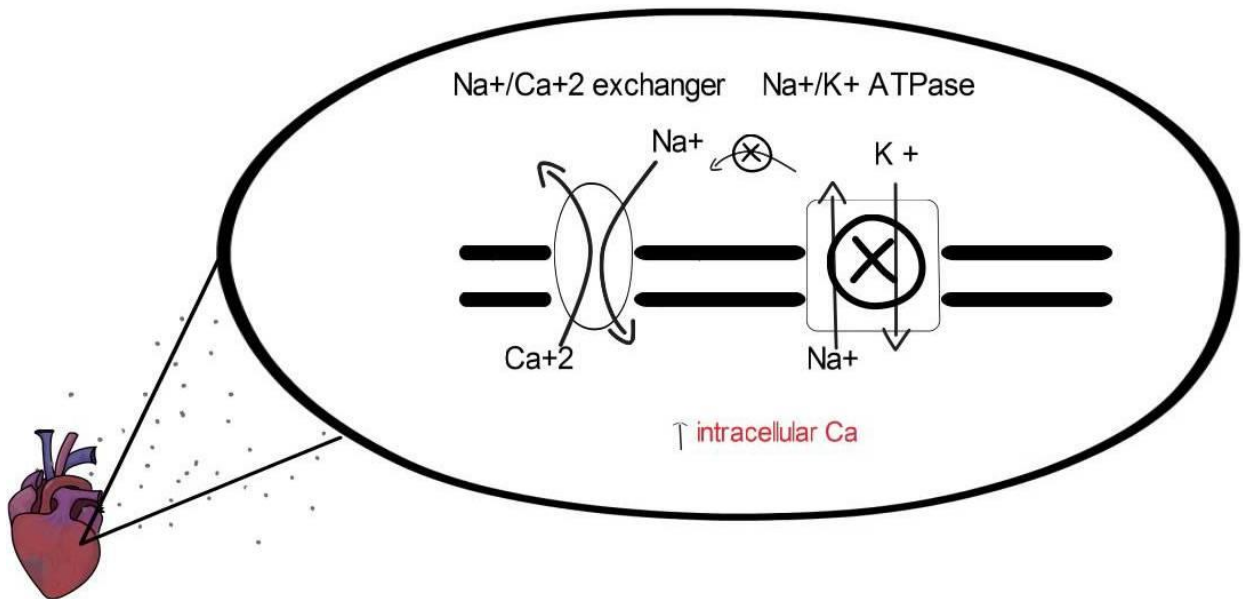
### **Pharmacokinetic of Digoxin poisoning:**

The pharmacokinetic of Digoxin poisoning vary including absorption of drug (can related to formulations [1], the oral absorption is about 60-80%, duration of distributions 2-6 hours, elimination half-life is about 20- 50 hours and elimination is predominantly renal so dose doses should be reduced in case of renal insufficiency [2]. The daily maintenance dose of Digoxin is about 0.125-0.5 mg. The therapeutic concentration of Digoxin is about 0.5-1.4 ng/ml and toxic concentration is about > 2 ng/ml. The duration of action of Digoxin is about 2-6 days. In acute Digoxin poisoning, the initial serum Digoxin concentration may be very high because of full distribution of Digoxin cannot occurs. The Digoxin undergo enterohepatic circulation so multiple dose of activated charcoal increase the clearance of Digoxin [2].

### **Mechanism of action and toxicity of Digoxin:**

It is generally considering that cardiac glycoside has identical mechanism of action, which is largely been described using Digoxin. However there may be difference in action between individual cardiac glycoside [3] and this may influence toxicity or response to treatment. Cardiac glycoside inhibits  $\text{Na}^+$ -  $\text{K}^+$  ATPase on cardiac and other tissue, causing intracellular retention of sodium ions, followed by increase intracellular calcium ions concentrations through the effect of  $\text{Na}^+$ - $\text{Ca}^{2+}$  exchangers. The elevated intracellular calcium ions concentrations promote inotrophy and bradycardia and intracellular accumulation of  $\text{Na}^+$  and  $\text{Ca}^{2+}$  causes partial membrane depolarization which increase automaticity and ventricular ectopic. Digoxin also increases the vagal tone, contributing to bradycardia and impaired conduction through the atrio- ventricular node, and may block the voltage gated sodium channel. Inhibitions of  $\text{Na}^+$ - $\text{k}^+$  ATPase are clearly involved in Digoxin

toxicity. At high dose there is depletion of intracellular of intracellular potassium ions and toxicity is partially reversed by infusion of potassium ions.



**Figure 1:** Mechanism of action of Digoxin

### Clinical feature of Digoxin toxicity:

Toxicity of Digitalis is high; margin of safety is low that is therapeutic index is about 1.5-3. Higher cardiac mortality has been reported among patient with steady state plasma Digoxin level greater than 1.1ng/ml. About 25% patients develop one or more toxic symptom. The clinical feature of Digoxin toxicity includes extra cardiac symptom and cardiac symptom are summarized in table-1. In about 2/3th of patient show toxicity, extra cardiac symptom precedes cardiac symptom and in rest of patient show serious cardiac arrhythmia are first manifestation.

Extra cardiac symptom includes Anorexia, Nausea, vomiting, diarrhoea, and abdominal pain is reported first due to gastric irritations, mesenteric vasoconstriction and Chemoreceptor trigger zone (CTZ) stimulations.

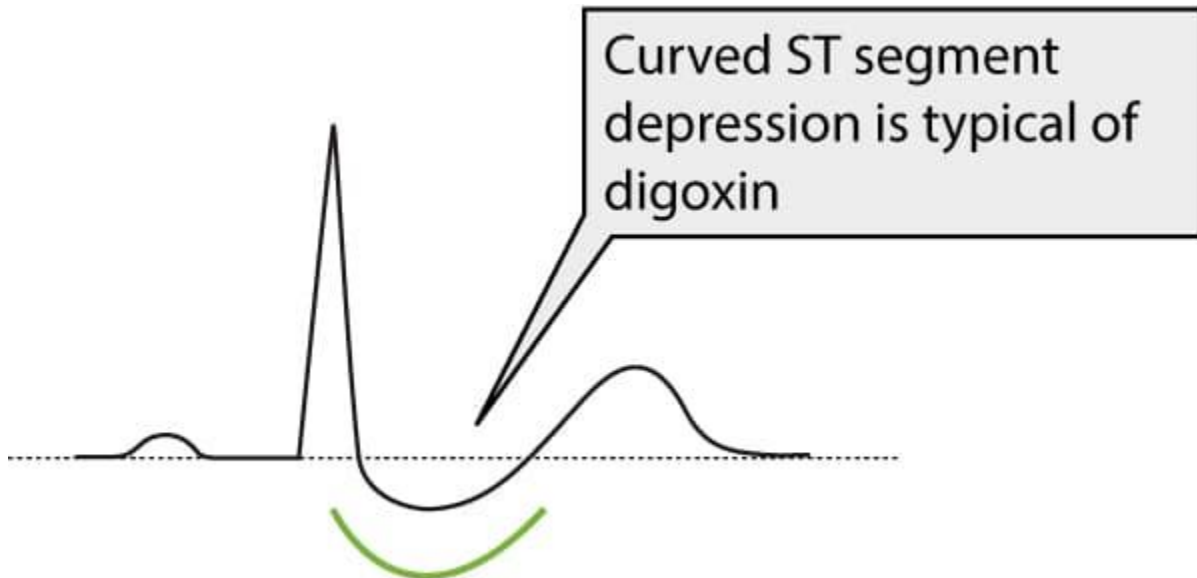
Cardiac symptom appears within few hours of acute poisoning. All most all type of arrhythmia can be produced by Digoxin overdose- pulsus bigeminus, several bradycardias, atrial extrasystoles, atrial fibrillation, nodal and ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation. Partial to complete AV block may be seen. The most common cardiac abnormality in Digoxin toxicity is sinus bradycardia. Restlessness, skin race and gynaecomastic are rare.

Extacardiac manifestation	Cardiac Manifestation
➤ Anorexia, Nausea, Vomiting	➤ Bradycardia
➤ Abdominal pain	➤ Ventricular tachycardia
➤ Diarrhoea	➤ ventricular fibrillation
➤ Altered visions	➤ Supraventricular tachycardia
➤ Fatigue	➤ Atrial extrasystoles
➤ Malaise	➤ Ventricular extrasystoles
➤ Headache	➤ Partial to complete heart block
➤ Mental confusion	➤ Atrial fibrillation
➤ Psychosis	➤ Nodal extrasystoles
➤ Skin rashes	➤ Multiple ventricular ectopic

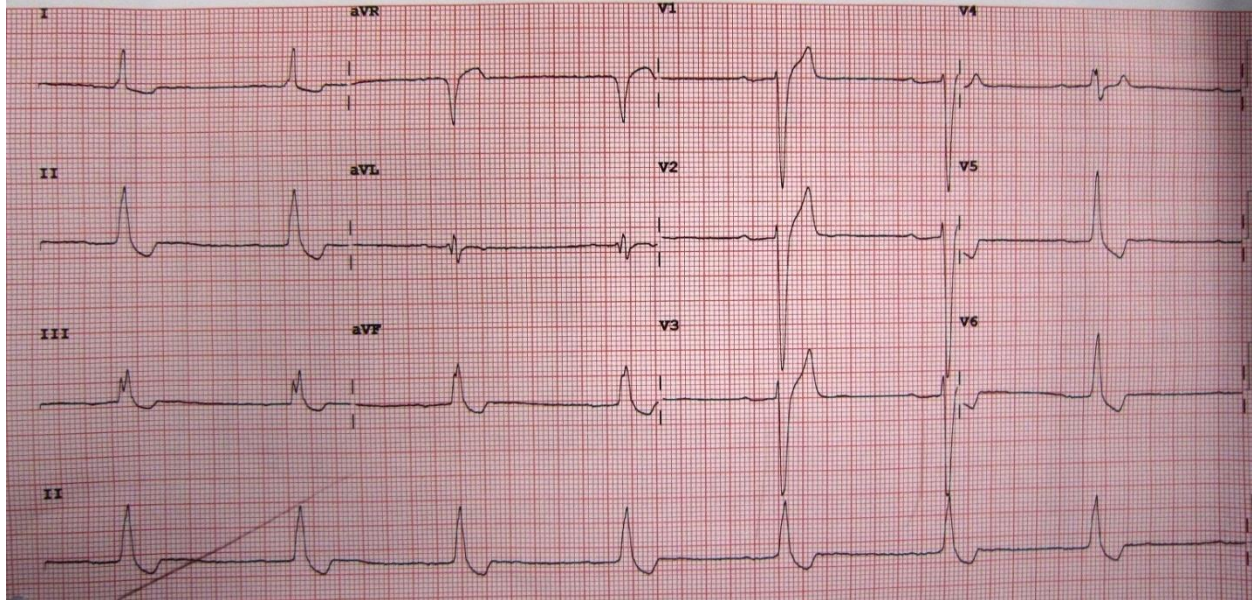
**Table 1:** Manifestation of Digoxin Toxicity

**Electrocardiogram change in Digoxin Toxicity:**

- ❖ The Electrocardiogram change in therapeutic doses or in mild toxicity included flattening or inversion of T wave and depression of the ST segment, shown in figure 2.
- ❖ The moderate poisoning manifested as Prolong PR intervals that is first degree heart block or sinus bradycardia.
- ❖ The severe poisoning manifested as second or third degree heart blocks due to inhibition of AV blocks. Sinus arrest is also reported. Death occurs due to ventricular fibrillation resistance to electrical cardioversion [4-8].



**Figure 2:** Typical ST-segment depression is seen in Digoxin toxicity.



**Figure 3:** Electrocardiography show typical ST-segment depression in acute digoxin toxicity.

### **Management of Digoxin toxicity:**

The management of patient with suspected or known cardiac glycoside poisoning is complicated by variable time in course in toxicity, unpredictable dose response relationship, and requirement for interhospital transfers and expensive or invasive treatment. A risk assessment regarding the likelihood of developing toxicity and planning treatment should be conducted in all patients with acute poisoning. In the case of cardiac glycoside poisoning this can be complicated due to variability in toxic dose. In case of Digoxin, ingestion exceeding 10 mg is often reported to be associated with severe toxicity and death in the absence of treatment but outcome data supporting this are limited and confounded by treatment received. Further dose of digoxin must be stopped at earliest sign of toxicity.

The main aim of treatment is to prevent the absorption of Digoxin in gastrointestinal tract, treatment of symptom like nausea, vomiting, abdominal pain and severe life threatening arrhythmia. The patient with acute Digoxin poisoning should be admitted in critical care area for continuous cardiac monitoring, investigations and consideration of treatment because there is a risk of development of significant life threatening arrhythmia, if u delayed in treatment. It is necessary to monitoring such patient up to 72 hours post ingestion. The toxicity is due to Digoxin poisoning usually manifests within 6 hours of last dose, whether this follow acute or chronic poisoning. If a patient is asymptomatic, ECG does not show bradyarrhythmias or tachyarrhythmia, potassium is within reference level and Digoxin concentration is less than 2.3 ng/ml, then risk of developing poisoning is low and patient is safe so can be discharged.

Hyperkalemia is manifestation of cardiac glycoside poisoning and though a higher potassium concentration is associated with increased risk of development of cardiac sign and symptom. In acute Digoxin

poisoning, Hyperkalemia is hallmark of poisoning [9]. In chronic Digoxin poisoning, there are many factors associated with Hyperkalemia such as renal failure, concurrent use of Angiotensin converting enzyme inhibitors or Angiotensin receptors blockers or spironolactone [10]. Hyperkalemia is associated with severe cardiac toxicity, with mean concentration of potassium 5.5mmol/ while potassium level 4.3mmol was found to be mild cardio toxicity. The Digoxin assay, in Digoxin exposures, higher plasma Digoxin concentration are associated with more severe poisoning but there are no specific criteria for diagnosing a patient as being poisoned. For example symptom of Digoxin toxicity was noted in some patient with Digoxin concentration is less than 2ng/ml but other with Digoxin concentration exceeding 2ng /ml [11].

### **Decontamination:**

Activated charcoal 50-100 mg should be given orally to all patients with acute ingestion of potentially toxic exposure, regardless of the time of ingestions. Although clinical trial has not confirmed the efficacy of this approach and this recommendation is based on pharmacokinetics data and safety of activated charcoal. A gastric lavage may be done in acute ingestions of poisoning to prevent absorption of Digoxin.

### **Electrolyte abnormality:**

Treatment of Hyperkalemia, if potassium concentration is more than 6 mmol/litre then give intravenous 50 ml 50% dextrose followed by 10 units' short acting insulin. Insulin may interact directly with  $\text{Na}^+ - \text{K}^+ \text{ATPase}$ , altering the effect of Digoxin as well as correcting Hyperkalemia by driving potassium into cells. Compared with control, there was marked improvement in survival with less cardio toxicity in rats administered insulin dextrose and difference in potassium (approximately 7mmol/L vs. 4.5mmol/L depend on model [12]. Hypokalemia may be noted in patient with Digoxin poisoning, related to either excessive diarrhoea or vomiting or medication such as diuretics. Hypokalemia should be corrected since it increases cardio toxicity from digitalis with therapeutic dose [7]. Hypokalemia should be corrected by infuse KCL 20 m.mol/hour intravenous. High extracellular potassium decrease binding of glycosides to  $\text{Na}^+ \text{K}^+ \text{ATPase}$  by favouring a confirmation of the enzyme that has lower affinity for glycoside and potassium tend to antagonize digitalis induced enhanced automaticity. Deaths have been reported in Hypokalemia patient. Exogenous calcium is given to stabilize the myocardium in Hyperkalemia is commonly recommended in past but at present the benefit or toxicity of exogenous calcium for the treatment of Hyperkalemia in case of cardiac glycoside poisoning is poorly defined and our practice is not to use it.

### **Treatment of arrhythmia:**

**Ventricular arrhythmia:** Intravenous Lidocaine is the drug of choice for ventricular arrhythmia. Lidocaine can suppress the excessive automaticity. Quinidine, procainamide and propafenone are contraindicated.

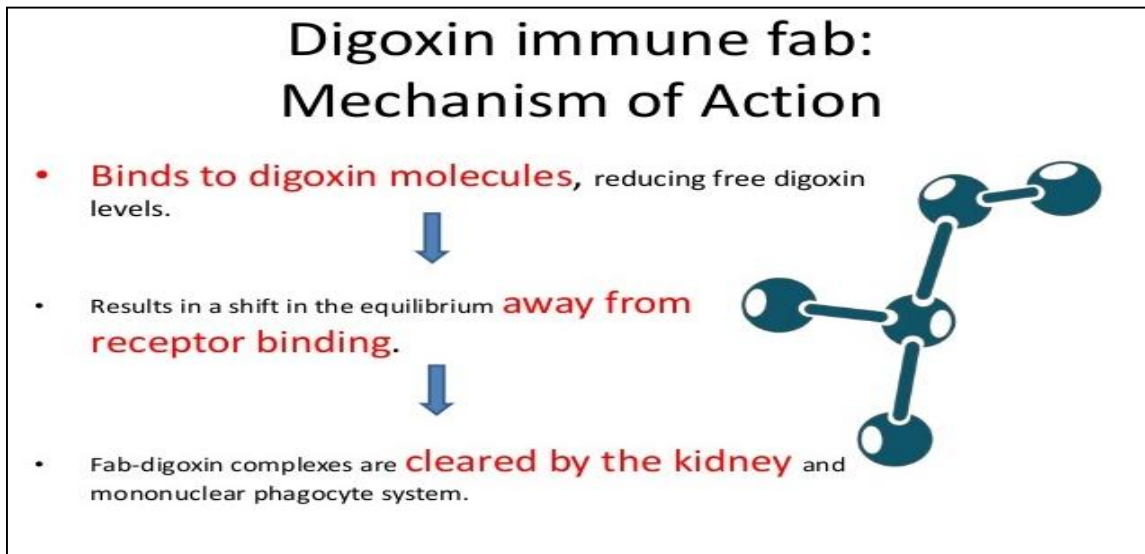
**Supraventricular arrhythmia:** Propranolol is given orally or injectable depend on urgency.

**Atrioventricular block and bradycardia:** injectable atropine 0.6mg- 1.2mg is given.

## Antidotes:

### Anti-Digoxin Fab:

Anti-Digoxin Fab has high binding affinity to Digoxin, removing it from  $\text{Na}^+\text{K}^+\text{ATPase}$  thereby reducing toxicity. Data on anti- Digoxin Fab in Digoxin poisoning are limited to observational data, so efficacy and indication is uncertain [13]. Recent observational data support an effect in acute poisoning but not so useful in chronic poisoning [10]. Anti -Digoxin Fab was found to be efficacious in binding the free Digoxin in central circulation, it appears to be minimally effective in alleviating cardiac toxicities in chronic Digoxin poisoning generally have significant co-morbid disease such as renal or cardiac failure and are medicated with drug such as beta blockers and calcium channel blockers. The lacks of response to Fab in such cases suggest these other factor could much of cardiac manifestation and risk of death. The dose regimens based on much lower initial dose have been proposed with 40 mg for chronic poisoning and 80 mg for acute poisoning. This can be repeated after 60 minute if inadequate responses or recurrence or there are therapeutics options to treat cardiac glycoside toxicity include pharmacological antagonist of bradycardia, reversal of  $\text{Na}^+ \text{K}^+\text{ATPase}$  inhibitions or enhanced elimination of cardiac glycosides. The role of antidotes for treatment of chronic Digoxin poisoning is less clearly.



**Figure 4:** Mechanism of action of Anti-Digoxin Fab.

### Atropine:

Atropine antagonizes cardiac glycoside vagal activation, increase heart rate and observational data suggest a benefit [6, 14]. Dose of 0.6- 1 mg are used first line, but dose as high as 2-3 mg have been used for persistent bradycardia. Although larger doses have been used [15] these may be associated with

anticholinergic delirium which requires sedative and nursing care. Hyperthermia may be hazardous in hot and non-air conditioned wards.

### **Temporary cardiac pacing:**

The temporary cardiac pacing is also treatment of choice for AV block and severe bradycardia. The temporary cardiac pacing is associated with more complication and death than anti-Digoxin Fab and it does not reverse Hyperkalemia. For example a retrospective series noted failure of pacing to prevent life threatening dysrhythmia in 23% of cases compared with 8% for Fab [8, 16]. Insertion of the pacing wire also triggers ventricular fibrillation. Other potential limitations of temporary cardiac pacing including procedure expertise and facilities are not available in rural region and in developing countries requiring interhospital transfer of patient and associated delay in treatment may be associated with death [6, 17].

### **Electrical cardioversion:**

Electrical cardioversion should be reserved for cases with ventricular arrhythmia refractory to other treatment using low energy level (20-100 J)[7]. Cardioversion with DC shock is contraindicated in patient with severe conduction defects.

### **Enhanced eliminations:**

Multiple dose of activated charcoal is recommended for toxic exposure to Digoxin because of pharmacokinetics data. Multiple dose of activated charcoal increase the clearance of intravenous Digoxin in volunteers by 47% in one study [18]. Multiple dose of activated charcoal decreased the apparent elimination half-life by nearly 50% in patient with chronic digoxin poisoning [19]. Multiple dose of activated charcoal doubles the clearance of intravenous digitoxin in volunteers [20]. Taken together it appears reasonable to administer multiple dose of activated charcoal, although it should not be used in preference to other treatment. Activated charcoal is safe but should not be administered to patient with an unprotected airways or ileus for example due to atropine treatment.

### **Other treatment:**

A range of other treatment have been trialled but data supporting an effect are limited and their use in routine clinical practice appears uncommon and data are limited to animal studies. These include anticalin, Fructose-1, 6-diphosphate (FDP), beta-adrenoceptor agonist (salbutamol) and magnesium for which evidence are limited. An anticalin with high binding affinity for digoxin reduced the free plasma concentration of digoxin and toxicity in rats [21]. Anticalins are non-biological alternative to anti-digoxin Fab but data in human are currently lacking. FDP is relatively cheap drug that increase the ATP production and stimulate  $\text{Na}^+ \text{K}^+$  ATPase activity.



## CONCLUSIONS

The incidence of digoxin toxicity is changed due to available of alternative drug for the treatment of congestive heart failure and atrial fibrillations. There is a range of options available for the treatment of digoxin toxicity like atropine, Anti-digoxin Fab, cardioversion and temporary cardiac pacing, their efficacy is poorly defined and this appears to influence their use in practice. More data are required to clarify the optimal treatment of cardiac glycoside poisoning, including the evaluation of lower priced medication that can be used in resource poor countries. Research priorities include improved understanding of the dose response of cheaper treatment such as insulin dextrose in humans.

## Abbreviations:

AV node: Atrioventricular node.

ECG: Electrocardiogram

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