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Updates in Digoxin Toxicity and Outcome of Management: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Cardiac glycosides, including digitalis and digoxin, have long-standing use in clinical practice. Digoxin has a half-life that varies from 36 to 48 hours, which may increase in cases of renal failure. Approximately 1% of Congestive Heart Failure patients treated with digoxin develop toxicity. The clinical features of toxicity are often non-specific. Diagnosis is difficult and usually made clinically, as levels of digoxin in the blood do not necessarily correlate with toxicity. Treatment involves early recognition and the administration of antibodies specifically against digoxin also known as Fab fragments. Digoxin concentration does not necessarily correlate with clinical symptoms of toxicity however digoxin concentrations may be used for calculating the amount of antidote therapy. Digoxin-specific antibody fragments are used when there is a risk of a life-threatening arrhythmia.

Keywords: Updates; evidence; digoxin toxicity; outcome of management.

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1. INTRODUCTION

Digoxin comes from the foxgloves plant known as Digitalis purpurea. It is a cardiotonic glycoside and belongs to the digitalis class. The chemical formula of digoxin is C_{41} H_{64} O_{14}. Cardiac glycosides, including digitalis and digoxin, have long-standing use in clinical practice [1]. This drug received approval from the FDA in 1954 and is used to treat various heart problems such as atrial flutter, atrial fibrillation, and heart failure with its associated symptoms and to induce fetal demise prior to an abortion. Superior therapies with milder adverse effects and better safety profiles have replaced it, such as beta-blockers and calcium-channel blockers. In current practice, it is reserved as a backup drug when first-line agents are ineffective [2]. Its optimal use is in the treatment of mild to moderate heart failure in adult patients and to increase myocardial contraction.

Digoxin is beneficial in patients with systolic heart failure, better known as heart failure with reduced ejection fraction (HFrEF), with an ejection fraction below 40%. However, it has no benefit in mortality reduction [3].

It is used for rate control in atrial fibrillation or atrial flutter when conventional therapies have not achieved the heart rate goal. Digoxin should not be administered in cases of pre-excitation caused by accessory pathways as digoxin induces atrial ventricular (AV) blockade and may trigger ventricular tachyarrythmias. It is ineffective in states of high sympathetic activity. Beta-blockers are preferable in such cases [4].

Supraventricular tachycardias that are not rate controlled by traditional therapies may benefit from digoxin.

Digoxin use has shown some success in the treatment of fetal supraventricular tachyarrhythmia [5]. The lowest effective dose should be administered to the mother as digoxin might cause uterine contractions and result in abortion. It is best to administer digoxin intravenously to achieve rapid digitalization. Intramuscular injections are highly discussed. No more than 2 ml of the drug should be injected at the same site. The injection should be made deep into the muscle, and the overlying area massaged post-injection. Intravenous injections are metabolized more efficiently than intramuscular injections and are the preferred route, as only about 80% of the drug is absorbed in intra-muscular injections as compared to intravenous dosing [6]. There is a risk of local irritation or myonecrosis. Digoxin has an oral bioavailability of approximately 75%, although intake efficacy might diminish when taking digoxin with high fiber foods. Some patients possess gut flora that metabolizes digoxin to dihydrodigoxin, thereby decreasing the drug's absorption. Macrolides interfere with normal gut microbiota, which normally metabolizes digoxin and can lead to higher absorbed concentrations. Metoclopramide decreases digoxin absorption [7]. Indomethacin and spironolactone decrease the clearance of the drug. Digoxin has two principal mechanisms of action which are selectively employed depending on the indication: (i) Positive Ionotropic: It increases the force of contraction of the heart by reversibly inhibiting the activity of the myocardial Na-K ATPase pump, an enzyme that controls the movement of ions into the heart. Digoxin induces an increase in intracellular sodium that will drive an influx of calcium in the heart and cause an increase in contractility [8]. Cardiac output increases with a subsequent decrease in ventricular filling pressures. (ii) AV Node Inhibition: Digoxin has vagomimetic effects on the AV node. By stimulating the parasympathetic nervous system, it slows electrical conduction in the atrioventricular node, therefore, decreases the heart rate. The rise in calcium levels leads to prolongation of phase 4 and phase 0 of the cardiac action potential, thus increasing the AV node's refractory period. Slower conduction through the AV node carries a decreased ventricular response.

Another use of digoxin is to induce fetal death before a second-trimester abortion. Digoxin kills the cells and poisons the tissues of the fetus [9].

The kidneys excrete digoxin in direct proportion to the glomerular filtration rate; the liver metabolizes 16 %. Digoxin has a half-life that varies from 36 to 48 hours, which may increase in cases of renal failure [10].

1.1 Study Objectives

The study aims to summarize the updated evidence regards digoxin toxicity and outcome of management.

1.2 Epidemiology

Approximately 1% of CHF patients treated with digoxin develop toxicity. Additionally, 1% of

adverse drug effects in patients greater than age 40 are due to digoxin toxicity; the incidence rises to greater than 3% in patients over age 85. Plant ingestions account for 80% of pediatric exposure; the remaining 20% of pediatric ingestions arise from medications. In general, ventricular dysrhythmias are more common in the elderly whereas supraventricular dysrhythmias are more common in children [11].

2. ETIOLOGY

Digoxin exhibits its therapeutic and toxic effects by poisoning the sodium-potassium ATPase. The subsequent increase in intracellular sodium leads to increased intracellular calcium by decreasing calcium expulsion through the sodium-calcium, cation exchanger. Higher intracellular calcium increases inotropy which can be of symptomatic benefit in CHF. At toxic levels, automaticity can be increased as well. Digoxin also increases vagal tone by decreasing dromotropy at the AV node. This can be used to control atrial tachydysrhythmias [12].

2.1 Outcome of Digoxin

The effect of digoxin is to increase intracellular levels of Ca (2+) ions and K + conductivity. Other effects of this drug are an increase in the refractory period of the sinus and AV nodes, a decrease in the atria and ventricles, and therefore an increase in excitability. It also reduces the transmission of electrical impulses through the AV node through vagal stimulation, resulting in a negative chronotropic effect [13].

Digoxin reduces the function of the α subunit of the Na (+) / K (+) - ATPase pump in cardiac muscle cell membranes by binding to them. The content of sodium ions in myocytes increases and, as a result of the sodium / calcium exchange function, intracellular calcium ions increase. A greater amount of Ca (2+) stored in the sarcoplasmic reticulum leads to greater contractility of the heart [7]. Digoxin is used with diuretics and ACE inhibitors in the treatment of congestive heart failure, particularly in patients with refractory symptoms, but it is ineffective in reducing morbidity and mortality while improving quality of life [14].

The safe therapeutic plasma level is 12.6 nmol / L. The plasma level of digoxin should be checked if toxicity or ineffectiveness is questioned. Plasma potassium levels should be monitored frequently. Due to the narrow therapeutic range, dose-dependent side effects (rare when the plasma concentration of digoxin is <0.8 µg / l) are common [15]. Hypokalemia increases risk because digoxin competes with K (+) to bind to the Na + / K + ATPase pump. Supportive care should be given in case of overdose. Digoxin antidotes are Digibind and Digifab, which are given for life-threatening arrhythmias or malignant hyperkalemia, which is defined as the inevitable rise in potassium levels due to paralysis of membrane-bound ATPase-dependent Na / K pumps mobile. ECG findings are increased PR interval, decreased QT interval, inverted T wave, and ST depression. Other changes include the rhythm of the AV junction and ectopic beats (bigemminia), which cause ventricular tachycardia and fibrillation [16].

Digoxin toxicity should be considered when deciding to start a new drug in a patient on digoxin therapy, especially in intensive care units where polypharmacy is not uncommon. Patients with acute cardiac glycoside toxicity and hyperkalemia, especially those with serum potassium levels greater than 5.5 meq / L, have a severe prognosis, but early and aggressive supportive therapy can significantly improve the outcome despite the lack Digifab availability [17].

2.2 Clinical Features

The clinical features of toxicity are often non-specific. They commonly include lethargy, confusion and gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhoea and abdominal pain). Visual effects (blurred vision, colour disturbances, haloes and scotomas) are rarer in contemporary practice. Cardiac arrhythmias account for most deaths [18].

Arrhythmias can occur even if the patient has no symptoms. Almost any arrhythmia can occur, with the exception of atrial tachyarrhythmias with a rapid ventricular response, because these usually require intact conduction in the atrioventricular node. Characteristic arrhythmias are those in which a tachyarrhythmia occurs simultaneously with sinus or atrioventricular node suppression, such as atrial and junctional tachycardia with atrioventricular block. However, sinus bradycardia, atrioventricular block and ventricular ectopy are more common [19]. With severe toxicity, ventricular tachycardia (which may be bidirectional) and ventricular fibrillation can occur. ‘Reverse tick’ T-wave inversion is not a sign of toxicity.

3. EVALUATION

The difference between toxicity and therapeutic range is small for digoxin and is determined to be between 0.5-2 ng/mL. Diagnosis is difficult and usually made clinically, as levels of digoxin in the blood do not necessarily correlate with toxicity. Digoxin is primarily cleared by the kidneys and declining renal function is a common cause of chronic toxicity. Therefore, renal function must be assessed [20]. Electrolytes must also be evaluated; hypokalemia, hypercalcemia, and hypomagnesemia are known to worsen the effects of toxicity. The inhibition of the sodium-potassium ATPase leads to hyperkalemia and can be used as a marker of toxicity severity. Serial electrocardiograms should be performed and the use of continuous cardiac monitoring may be considered as fluctuation in rhythms is commonly seen. EKG findings sometimes referred to as the digitalis effect may be seen. These changes commonly involve the T wave and include flattening, inversion, scooped appearance of ST-segment and ST depression in the lateral leads [21].

It is important to know that endogenous digoxin like immunoreactive proteins can result in a false-positive result. This is more likely to occur in patients with: Liver or renal disease, chronic heart failure, subarachnoid hemorrhage, acromegaly, diabetes or pregnancy.The other problem is that there are several types of assays to measure digoxin and its metabolites, but these assays do vary in sensitivity. Further, the tests are hampered by cross-reaction with steroids and cholesterol-like substances [22].

4. MANAGEMENT

Treatment involves early recognition and the administration of antibodies specifically against digoxin also known as Fab fragments. Digoxin concentration does not necessarily correlate with clinical symptoms of toxicity however digoxin concentrations may be used for calculating the amount of antidote therapy. Although guidelines are unclear, treatment with digoxin immune Fab is also known by the trade name Digibind, is considered first-line therapy for dysrhythmias including AV block and ventricular tachycardia caused by suspected digoxin toxicity [23]. Fab fragments are highly effective in binding the digoxin molecule with minimal detrimental side effects. The antibody fragments form complexes and are secreted via the urine. Empiric treatment consists of 10 vials of Fab fragments for adults and five vials for children. Treatment with digoxin-specific antibodies will lead to hypokalemia, and serum potassium should be monitored frequently. Activated charcoal can be considered in the treatment of acute ingestion within two hours. Further treatment is supportive. More research is needed for optimal dosing and whether or not the use of digoxin-specific antibodies are cost-effective for use in non-life threatening toxicities.

Hydration, oxygenation, and close monitoring are necessary. The ECG has to be continuously monitored for dysrhythmias. All electrolyte disturbances need to be corrected [24].

One should remember that if digoxin is neutralized with antibodies, the patient may develop heart failure and lead to worsening of the arrhythmias. Other issues related to the antibody include serum sickness and anaphylaxis [25].

Supraventricular need to be managed with short-acting beta-blockers. Phenytoin has been shown to suppress digoxin induced tachyarrhythmia. Another option is lidocaine when managing ventricular arrhythmias. Atropine may be used to manage bradycardia. The use of magnesium is not recommended as it can worsen bradycardia or an AV block. Cardioversion is not recommended as it can precipitate ventricular arrhythmias; instead, defibrillation may be used according to ACLS protocol [26].

4.1 Precautions and Adverse Effects

Hypomagnesaemia and, more importantly, hypokalaemia (common with diuretic use) should be corrected before or during administration because digoxin-specific antibody fragments will further lower potassium. Hypokalaemia occurs as a result of treatment in about 4% of patients. Serum potassium should be frequently monitored [27].

'Rebound' toxicity is the reappearance of toxicity after an initial response to digoxin-specific antibody fragments. This occurs in about 2% of patients given a full neutralising dose. It can develop 12–24 hours after treatment, but up to 10 days later in patients with renal failure. Serum digoxin concentration is of no use in diagnosis, because it measures the digoxin in the complexes with antibody fragments as well as unbound digoxin. The concentration therefore rises many fold after digoxin-specific antibody

fragments are given even in the absence of rebound toxicity [28].

Heart failure or atrial fibrillation with rapid ventricular response (presumed re-emergent due to removal of digoxin effect) occurs in up to 3% of patients. Allergic reactions occur in about 1% of infusions [29,30].

5. CONCLUSION

The clinical features of toxicity are often non-specific. Diagnosis is difficult and usually made clinically. Treatment involves early recognition and the administration of antibodies specifically against digoxin also known as Fab fragments. Digoxin concentrations may be used for calculating the amount of antidote therapy. Digoxin-specific antibody fragments are used when there is a risk of a life-threatening arrhythmia.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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