Review Article

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20212830

Systematic treatment and prevention of cardiac digoxin toxicity

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Received: 08 July 2021 Accepted: 24 July 2021

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ABSTRACT

Digoxin has a narrow therapeutic index, such as complicated pharmacokinetics and dynamics. Many drug interactions may occur when the administration of one drug alters the clinical effects of another. As a result, digoxin toxicity can be a common condition within clinical settings that might lead to the development of many morbidities and even mortality. Many studies were published to investigate the efficacy and safety of different management modalities to enhance the outcomes that follow digoxin administration. The aim of the study was to discuss the approaches to systematically treat and prevent the development of cardiac digoxin toxicity. The findings are based on evidence from previous studies in the literature. To be specific, Fab fragments are the most effective modalities that can be used to treat severe cases within ideal periods. However, evidence regarding their administration for asymptomatic or mild cases is still poor regarding the cost-efficacy and the development of serious adverse events. Physicians should primarily care for a better intervention as it is usually associated with a significantly more enhanced prognosis and clinical outcomes. Nevertheless, adequate monitoring of the patients and evaluation of their personal and medical history are important steps in the process, and further approaches are still needed. Also, detailed information about our intended outcomes is furtherly discussed within the manuscript.

Keywords: Digoxin, Cardiology, Toxicity, Management

INTRODUCTION

Although digoxin is a very old drug, it is still used, and it is indicated within the global guidelines for managing heart failure. ¹⁻³ However, it is not usually used as a first-line drug because of the reduced safety and efficacy profiles. ^{4,5} This is attributable to the narrow therapeutic index of the drug, the complicated pharmacokinetics and dynamics, and to many drug interactions that may occur when administering it. As a result, digoxin toxicity can be a common condition within clinical settings that might lead to the development of many morbidities and even mortality.

A previous investigation by Budnitz et al.⁶ has shown that the causes for hospitalization are due to drug interactions. Digoxin toxicity was the 7th most common cause between 2007 to 2009 within the American clinical settings (Figure 1).

Many studies were published to investigate the efficacy and safety of different management modalities to enhance the outcomes that follow digoxin administration. The aim of the study was to discuss the approaches to systematically treat and prevent the development of cardiac digoxin toxicity. The findings was based on evidence from previous studies in the literature.

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Features	Acute Digoxin Toxicity	Chronic Digoxin Toxicity
Age	Younger	Older
Cardiovascular status	Normal myocardium	Underlying cardio- vascular disease
Digoxin level	High	Normal to high
Potassium level	Normal to high	Normal to low
Symptoms	Cardiac symptoms pre- dominate	Noncardiac symp- toms predominate
Types of car- diac symp- toms	Atrioventricular conduction blocks common	Various dysrhyth- mias

Figure 1: Characteristics of acute and chronic cardiac digoxin toxicity.⁴⁷

METHODS

This literature review was based on an extensive literature search in Medline, Cochrane, and Embase databases on 28th June 2021 by using the medical subject headings (MeSH) and a combination of all possible related terms. This was followed by the manual search for papers in Google Scholar and the reference lists are included at the end of this research.^{7,8} This literature review discusses the cardiac digoxin toxicity were screened for relevant information, with no limit placed on date, language, age of participants, or publication type.

DISCUSSION

Management of digitalis toxicity

The most serious manifestations that follow digoxin toxicity are the acute ones that are related to cardiac rhythm disturbances. therefore, adequate and early management of these manifestations is a priority in such situations. For instance, it was previously demonstrated that a temporary pacing and intravenous atropine should be administered in patients suffering from an atrioventricular block. On the other hand, phenytoin and lidocaine should be administered in cases of ventricular arrhythmias.9-12 In another context, recent investigations have indicated the validity of more efficacious compounds (antibody Fab fragments for digoxin toxicity). Consequently, these treatment regimens are no longer administered in such situations. Colestyramine, activated charcoal, and colestipol have been validated as efficacious management modalities in such situations, which have been proven to be acting by binding to digoxin within the gastrointestinal tract and reducing its absorption. 13-16 This has significantly lead to an increase in the systematic clearance of the compound. In addition, it enhanced excretion within the stool. It should be noted that the elimination of digoxin with these drugs is a very long process. Therefore, they should only be considered in asymptomatic or mild cases when early or life-saving measures are not usually indicated. In 1976, the first report about the potential therapeutic effects of Fab fragments in reserving digoxin toxicity, and the fragments were effectively obtained from sheep antiserum and are obtained as the Fc portions. The main advantages of this approach over using IgG antibodies against digoxin are that: (1) increased extravascular distribution, (2) reduced events of allergic reactions and immunogenicity, (3) facilitated renal clearance and enhanced elimination from the systemic circulation. Trials have reported that Fab fragments against toxic digoxin compounds are 80-90% effective in reducing the clinical manifestations of the present toxicity. 19,20

Furthermore, it was demonstrated that the favorable events were obtained 4 hours following the administration of the modality.¹⁹ On the other hand, cases with reduced effectiveness are probably attributable to the administration of inadequate doses due to a wrong diagnosis of the condition. Nevertheless, it should be noted that some clinical settings and healthcare facilities might not afford anti-digoxin Fab which add to the limitation of the modality. Accordingly, further investigations are needed for further validation of the modality, especially in non-severe situations to indicate whether or not antidigoxin Fab fragments should be used to manage these conditions.^{21,22} It has been discovered that the affinity of the digoxin compounds to the Fab fragments is even higher than the affinity of the compound to the occurring physiological compounds within the human body, leading to reduced intensity and development of the clinical manifestations. Accordingly, a rapid redistribution of the digoxin compounds occurs after the administration of the Fab fragments, leading to reduce intracellular toxic digoxin compounds. The antitoxic effects of the Fab fragments have been reported to occur within minutes, with a plasma $t^{1/2}$ of 12-20 hours within patients that have normal kidney functions. However, it has been reported

that the aforementioned t^{1/2} period usually increases ten times in patients suffering from impaired renal functions. ¹⁸ Although the estimated volume of distribution for the compound was estimated to be 0.4 l/kg, many investigations have demonstrated the potential development of some adverse events that might furtherly complicate the affected cases. ^{18,20,23,24} Some allergic adverse events can develop secondary to the administration of the modality. However, it should be noted that no anaphylaxis events were reported.

Following the neutralization effect of the compound against digoxin toxicity, many secondary adverse events as hypokalemia, heart failure exacerbation, ventricular acceleration in patients suffering from atrial fibrillation because of the restored activities of Na+-K+-ATPase following the reduced actions and elimination of digoxin. A previous trial reported that early hypokalemia was observed in 4% of the participants following Fab administration.¹⁹ Rebound digoxin toxicity can also be another adverse event, especially when the nutrient dose of Fab is less than half of the optimal recommended dose.²⁰ Therefore, adequate and frequent monitoring of the digoxin levels after the administration of Fab fragments is an essential part of achieving adequate management. Additionally, there is a need to prevent the development of any surprising adverse events that can lead to serious complications. Furthermore, studies have suggested that patients with impaired renal functions (creatinine clearance <50 ml/min) and high serum digoxin levels (>3.6 nmol/l) should be indicated to receive anti-digoxin Fab fragments hoping to reduce the length of hospital stay and enhance the economic burden. Frequent monitoring of the patient's condition and cardiac status to provide adequate oxygenation and hydration, and properly managing any potentially present electrolyte imbalance.

In cases where anti-digoxin Fab fragments are not available or contraindicated, other management modalities should be considered based on the underlying pathology and clinical manifestations. For instance, using short-acting beta-blockers is favorable in the management of supraventricular arrhythmias. Phenytoin has been used to enhance the tachyarrhythmias that develop with digitalis toxicity. Bradycardia can be managed by using atropine, and lidocaine can also be used for the management of ventricular arrhythmias while using magnesium is not favorable because it might aggravate any potentially present atrioventricular block or bradycardia. Besides, it should be noted that using cardioversion should not be recommended as it might induce pathological arrhythmias. Therefore, defibrillation should be rather used. 25,26

Prevention

There is no doubt that adequate prevention of digitalis toxicity is much better than treating it. Drug transcription, administration, ordering, monitoring, or dispensation are all actions that can lead to adverse drug reactions and potential development of digitalis toxicity.²⁷ Nevertheless,

evidence shows that up to 69% of the currently known adverse drug interactions can be effectively prevented. ²⁸⁻³¹ Accordingly, the majority of cases with digitalis toxicity can be effectively prevented because such events usually result from the administration of inappropriate doses in patients that are usually suffering from renal impairment or in cases of adverse drug interactions. ³²

Studies have reported guidelines that can be followed by physicians and managing clinicians to decide the optimal suitable doses for the prevention of digitalis toxicity. For instance. Jelliffe et al.³³ reported that to achieve a stable concentration of digoxin of 1.4 µg/l, the administration of digoxin should be initiated at 50% of the initial dose, being 0.125 mg/day rather than 0.25 mg/day. Moreover, when other drugs that are known to interact with digoxin, like amiodarone, are indicated, the dose of digoxin should be reduced to 50% as previously mentioned or by maintaining the dose but changing the intervals when it should be administered. Technological advances in the medical field have led to the innovation of clinical decision support modalities that might help physicians to intervene against the development of digitalis toxicity by planning the right dosage systems according to the patients' medical profiles, and by avoiding drugs that can lead to the development of serious drug interactions that might exacerbate the toxicity of digitalis. 34,35 However, these modalities are not widely available, especially in areas with low socioeconomic characteristics and poor technological advances. Accordingly, adequately training physicians to manage such cases and appropriately deal with digitalis administration is inevitable to achieve better interventions and enhance patients' outcomes.

It should be noted that many issues should be considered before the administration of digoxin to reduce the chances of toxicity occurring. At first, the clinician should adequately assess the different variables of the patient before starting to administer digoxin, including age, body habitus, medical history, renal functions, and the presence of comorbidities. Studies have indicated that older patients are more liable to digoxin toxicity because the kidney and liver functions deteriorate in these patients, which can significantly impact the metabolism and elimination of digoxin from the body. 39,40

Adequate assessment of the dose and choosing it based on the body mass index and weight of the patient is also essential because digoxin is a highly hydrophilic compound. Adequate monitoring of the different electrolytes is also recommended to be routinely performed because some electrolyte disturbances as hypercalcemia, hypomagnesemia, hypokalemia, and hypernatremia might exacerbate the actions of digoxin on the cardiac muscles. Patients with exacerbated chronic heart failure might also suffer from reduced clearance of digoxin from their sera, leading to digoxin toxicity. Chronic pulmonary disease-induced alkalosis and hypoxia might also stimulate a state of body toxicity that might alter digitalis toxicity. Altered pharmacokinetics of digoxin

might also be another potential etiology for digoxin toxicity, as hyperthyroidism might increase the volumes of clearance and distribution while hypothyroidism can reduce them. 41 Moreover, a previous study reported that being previously hospitalized for digitalis toxicity might be a risk factor for another episode. 44

Besides, as previously mentioned, assessing the medication history of the patient is also essential before inaugurating the administration of digoxin, because some drugs might be directly or indirectly associated with significant alterations in the kinetics and dynamics of the drug, jeopardizing the patient to develop toxicity. Adverse drug reactions might lead to the accumulation of digoxin within the blood, and increasing the chances of toxicity. Many drugs were previously reported according to many investigations to have unfavorable adverse events when administered with digitalis. 45 Interesting adverse reactions were reported with the administration of macrolide antibiotics, as clarithromycin, which has been reported to be responsible for the elimination of gut bacteria, that is responsible for inactivating digoxin, as estimated in up to 15% of the general population. 36,43,46

Furtherly, we would indicate that assessment of renal functions is an important step in such situations, and therefore, physicians should adequately monitor and take care of creatinine clearance levels, because the kidneys have essential roles in the development of digitalis toxicity, being mainly responsible for eliminating the drug from the body.

CONCLUSION

This literature review was based on evidence from previous studies in the literature, and it discusses the approaches to systematically treat and prevent the development of cardiac digoxin toxicity. Fab fragments are the most effective modalities that can be used to treat severe cases within ideal periods. However, evidence regarding their administration for asymptomatic or mild cases is still poor regarding the cost-efficacy and the development of serious adverse events. Physicians should primarily care for a better intervention as it is usually associated with a significantly more enhanced prognosis and clinical outcomes. Adequate monitoring of the patients and evaluation of their personal and medical history are important steps in the process. Further approaches are still needed.

Funding: No funding sources Conflict of interest: None declared Ethical approval: Not required

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Cite this article as: Alshaer OR, Binobaid AO, Mofti AH, Sadagah MM, Olwi KM, Alsulaiman AS, et al. Systematic treatment and prevention of cardiac digoxin toxicity. Int J Community Med Public Health 2021;8:4056-61.