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The Effectiveness of Digoxin in Treating Heart Failure

Abstract

According to the CDC, about 5.7 million Americans have congestive heart failure (CHF) and half of those diagnosed will die within five (5) years. In addition, there is an exorbitant cost associated with heart failure, an estimated $30.7 billion yearly [1]. Katzung, states that positive inotropic drugs are effective for acute heart failure, however, other research have shown that non-cardiac dugs can be more effective for long-term treatment of heart failure [2]. Recent studies have discussed the role of digoxin as a management therapy rather than justfor acute treatment of heart failure. Digoxin is a cardiac glycoside, derived from tropical plants (Digitalis lanata and D purpurea) [2]. The mechanism of action of digoxin involves stabilizing the sodium and potassium ion as they cross the plasma membrane in opposite directions using the Na-K-ATPase. The pharmacokinetic and pharmacodynamics of digoxin is necessary to determine the appropriate treatment based on patients clinical presentation; details such as the hemodynamic effect, neurohormonal effect, and the electrophysiology effect will be discussed to help in designing appropriate therapy [3].

Research Article

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Introduction

The incidence and prevalence of congestive heart failure (CHF) have increased in recent years [4], with 5.8 million in the US and 23 million worldwide [1]. This growth correlates with increase awareness of heart failure, the aging population, or perhaps improvement in management and treatment of the disease [4]. Studies identified disparities that may exist in mortality rates of patients such as race, ethnicity, sex, hospitalization, and socioeconomic status [4]. Also, women were hospitalized more frequently with CHF than men. Risk factors such as ischemic heart disease, hypertension, the Framingham study indicated that 75% of the participants with heart failure had associated hypertension [4]. Other risk factors includes diabetes, smoking, dyslipidemia, obesity, and renal failure, these are contributing factors to patients with heart failure [4]. Heart failure is a major clinical and public health problem which has led to significant health care expenses, mortalities and morbidities [5].

According to the CDC, the US spends an estimated $30.7 billion each year, this includes a combined cost of health care services, medications, and missed days at work [1]. This exorbitant cost of heart failure has been an economic burden on the health care system [6]. The cost rises as the aging population rises and the lifetime cost after diagnosis of heart failure increases [6]. The lifetime cost after diagnosis of heart failure can be attributed to the effectiveness in treatment of digoxin.

Lee et al. [7] conducted a randomized trial to determine the effectiveness of digoxin in treating patients with heart failure. Oral digoxin and a placebo was used in 25 outpatients, it was determined that patients with more severe or chronic heart failure responded fairly to the treatment of digoxin Lee et al. [7]. Based on this study, it is stated that digoxin is beneficial in treating heart failure Lee, et al. [7]. Researchers have compared the use of various drugs with digoxin to determine its effectiveness in treating heart failure. In 1989, DiBianco compared oral milrinone, digoxin, a combination of both, and placebo in 230 patients with moderately severe heart failure [8]. The study stated that milrinone, andits combination with digoxin was able to improve heart failure more than digoxin alone. In essence, digoxin was considered as effective as any other drugs used to treat heart failure [8].

Ho, et al. discussed the diagnostic criteria used by the Framinigham study; this includes two major or one major and two minor criteria, unlike other studies which presented no precise criteria or limited criteria to diagnose CHF [9]. This criterion was used to estimate the incidence and prevalence of CHF. The study found that hypertension and coronary heart disease were prevalent conditions in patients with heart failure, since 78% of women with hypertension had an increased incidence in heart failure and 59% of men with coronary heart disease had an increase prevalence of heart failure. However, the diagnosis of CHF includes a constellation of symptoms that may vary from patient to patientSubsequently, Hall,et al, stated that males have higher risk factors, and they do not utilize health care services, therefore, conditions that may predispose to CHF are left undiagnosed and untreated. Male patient are hospitalized for CHF because the disease may have progressed significantly and requires immediate treatment. Hospitalization for males with CHF under age 65 has increased by 21% from 2000 to 2010, compared to male 65 years and over, the rates did not change [10].

Another aspect of digoxin is the effect of excitable tissue; the inhibition of Na-K-ATPase depolarizes and increases spontaneous activity in neuron and smooth muscle cells. In addition to the effect on the heart, the gastrointestinal tract is a common site for digoxin toxicity, which presents with nausea, vomiting, anorexia, and diarrhea. In the central nervous system, the chemoreceptor trigger zone and vagal is stimulated. As calcium levels increases

during the inhibition of Na-K-ATPase, magnesium levels decreases which is a risk factor for arrhythmia [2].

Pulmonary hypertension is one of the common comorbidities in heart failure patients. Based on retrospective study of the DIG trial, it was determined that the adverse effects of digoxin were problematic [11]. The discussion highlighted the fact that patients taking digoxin had an increased risk for arrhythmias, but it clearly stated that risk of death was reduced [11].

Mechanism of action of Digoxin

The cardiac cell needs the Na-K concentration to generate an action potential; the na-K crosses the plasma membrane with the help of Na-K–ATPase or sodium-potassium pump [12]. Cardiac glycosides inhibits Na-K- ATPase, which led to increased extracellular potassium for which hyperkalemia or hypokalemia can affect function of the cardiac cell, also, an increase intracellular Na concentration, will slow down Na/Ca exchanger which in turn will promote increase intracellular Ca concentration [12].

It is stated that digoxin produces a unique constellation of effects on the cardiovascular system; such as increase force of contraction (positive inotropic effect), a decrease in heart rate (negative chromotrophic effect), and a decrease in conduction velocity (negative dromotrophic effect or vagomimetic effect) [2]. In addition, digoxin may also increase parasympathetic tone, while reducing sympathetic tone [13]. Sodium and potassium are regulated inside the cell by the enzyme Na-K-ATPase which is inhibited by digoxin, thus leads to increased intracellular Na and Ca. There are various effects of digoxin both direct and indirect, whose primary concern is to improve the functionality of the heart during a period of heart failure. The consequences include increase in force or velocity of myocardial contraction, and neuronal deactivation effect.

Hemodynamic effect of digoxin

A study was conducted to determine the hemodynamic effect of digoxin on chronic heart failure. The participants of the study included patients with decreased contraction force and mechanical impaired left ventricle filing. The result of the study was significant in that it suggested the positive inotropic effect of digoxin with decreased pulmonary capillary pressure, and a decrease cardiac index [14]. The hemodynamic effects of digoxin in heart failure includes; increase cardiac output, decreased capillary wedge pressure, increased left ventricular ejection fraction (LVEF) [15]. A well-known study such as PROVED was a digoxin withdrawal study which resulted in worsened heart failure and a decrease in LVEF [15]. Another study, the RADIANCE trial which included the role of digoxin in patients who were also taking diuretics and ACE-Inhibitors examined the withdrawal effect on the patients. It was revealed that patient's conditions deteriorated upon withdrawal of digoxin and there was a decrease in LVEF, increase in heart rate and increase in body weight [16]. Ultimately, the triple therapy of digoxin, ACE-Inhibitor, and diuretic patients had a better outcome in heart failure [16].

Neuro-hormonal effect of digoxin

The neuroendocrine system is activated in patients with heart failure, this correlates with an increase in sympathetic neural outflow which results in the release of atrial natriuretic peptide (ANP). Release of ANP inhibits vasoconstrictor effects, sensitizing the baroreceptor, and inhibiting the activation of renin-angiotensin-aldosterone system [17]. Among the many benefits of digoxin is the neurohormonal effects which in part affects the baroreceptor function which decreased activation of sympathetic nervous system, also increase vagal tone, sympathoinhibitory effect, decrease norepinephrine concentration and plasma renin activity. Low dose of digoxin or increase therapeutic dose may impact neurohormones, and perivascular fibrosis may be prevented by digoxin. Administration of triple therapy is associated with improvement in prognosis of heart failure [17].

Electrophysiological effect of digoxin

In a study by Sticherling et al. [18], examine the electrophysiological changes by assessing the atrial refractory on patients taking digoxin [18]. The study concluded that digoxin shortens atrial effective refractory period (ERP) which predisposes to further atrial fibrillation episode in patients with atrial fibrillation [18]. The electrophysiological effects of digoxin include parasympathometic action on atrial myocardium, slow conduction and prolong atrioventricular node refractory period, with no effect on purkinji system [19].

Pharmacokinetic and pharmacodynamics of digoxin

Pharmacokinetics of digoxin examines the absorption, distribution, metabolism, and excretion of digoxin [2,20]. Digoxin is commonly used in elderly patients with heart failure or arrhythmia. Since aging is associated with physiological changes of the body, which may impact the pharmacokinetic of the drug. Therefore, it is necessary to monitor and manage therapeutic dose of the drug. Aging leads to altered absorption, in that there is a decreased amount of saliva produced, hence, reduces the oral absorption of digoxin. Drug distribution in the elderly is dependent on organ perfusion and changes in body composition [20]. Drugs are metabolized in the liver along with the kidney and lungs; however, liver metabolism is decreased with age. In addition, kidney function maybe be reduced with age, hence decrease the elimination rate. Digoxin has a narrow therapeutic index which means that it will put patients at risk for severe toxicity [20].

Pharmacodynamic effect of digoxin

Digoxin has both therapeutic and toxic effects, which can directly or indirectly affect the cardiovascular system, central nervous system, and gut [2]. Curie et al. [20] discussed the benefits of digoxin such as cognitive improvement seen in patients taking digoxin [20]. Cognitive dysfunction is a comorbidity seen in heart failure patients, therefore, digoxin therapy relieves the symptoms of cognitive dysfunction in elderly patients. Molecularly, digoxin inhibits Na-K-ATPase, which is an enzyme used to transport sodium and potassium across the membrane, it's called the sodium pump [2]. This sodium pump is necessary to maintain the normal resting potential; however, the drug digoxin inhibits this process. Inhibition of Na-K-ATPase results in an increase in intracellular sodium concentration, also, the reduction in calcium contributes

to the increase intracellular sodium, as a results increases cardiac contractility [2]. The increased intracellular calcium leads to increase potassium conductance which results in decrease action potential. Autonomic action of digoxin involves both sympathetic and parasympathetic which predominates, such as the atropine-blockade effects of digoxin. This innervation affects the atrial and atrioventricular nodes, more than the purkinji or ventricular function [2].

Digoxin intoxication

Cardiologist, Pincus, stated that digoxin dosage has been reduced over the past decade; the new recommended range to treat heart failure is 0.5 to 0.9 ng/ml^3. Although, the recommended range is lowered, there has been a decline in digoxin use, hence digoxin toxicity [21]. In a study by the Australian Institute of Health, stated that chronic toxicity is more common. Patients are usually given antidote or treatment for any drug overdose or toxicity; however, there is no recommended guideline to treat mild to moderate digoxin toxicity [21]. Digoxin-specific fab antibody fragment is used to treat severe toxicity for which patients may present with life threatening arrhythmia, cardiac arrest, hyperkalemia [21]. Digoxin-specific fab antibodies have high affinity for digoxin and will reverse its toxicity. Although, these antibodies are expensive, they are also proven most effective, for which studies have shown that 80% of patients have been completely resolved of all digoxin toxicity [22]. However, in the case of severe toxicity with cardiac involvement digoxin-specific fab fragment should be administered immediately [22].

Activated charcoal is another effective agent used to treat digoxin toxicity. It is useful for patients with recent overdose, or in event where digoxin-specific antibody is not available, also no cardiac involvement [22]. Activated charcoal may increase clearance of digoxin by binding to digoxin in the intestinal lumen and gastrointestinal dialysis. Other drugs such as colestipol and cholestyramine will bind to digoxin in order to be eliminated from the system. Important to note, activated charcoal is unpalatably and can cause severe nausea, vomiting and a risk of aspiration, therefore, assessing the quantity and reason for the overdose is necessary [22].

Dosing rate exceeding 3.1 ng/ml^3 is considered therapeutic overdose, during which patients may present with both cardiac and extra cardiac manifestation [19]. In a case report, Gowda et al., described the similarities in presentation of a toad venom and that of digoxin toxicity, although, the patient died before administration of digoxin specific gab fragment. It is stated that the treatment is also effective in treating toad venom exposure.

Digoxin toxicity can also occur with drug-drug interaction such as diabetic patients treated with sulfonureas who may be treated simultaneously with clarithromycin. Hyperkalemia is a presentation seen in digoxin toxicity, which is also seen among patients treated with ACE-Inhibitor and potassium sparing diuretics, this combination can lead to life threatening hyperkalemia [23]. Drug-drug interaction is of major concern with elderly patients with several co-morbidities, treated by multiple physicians, and accidental combination of multiple drugs. Drug interaction can also be alarming with numerous hospital admissions in that patients are not informed of their list of medications and can lead to drug intoxication [23]. It is stated that with computerized prescribing system, the incidence of digoxin toxicity will be decreased since there are prompt alert to potential clinical error [24].

Drug intoxication in elderly can also be related to impairment of renal function, digoxin is excreted from the body by the kidney and if impaired the patient may have an increase amount of digoxin in the plasma. Elderly patients can be affected with decreased volume of distribution, seen in patients' cardiac dysfunction and renal impairment [22]. Drug toxicity is seen in 35% of patients, and careful management of this condition is essential, in that, the severity of the problem should be carefully assessed and the reasons for toxicity should be discussed to determine whether it was accidental or deliberate overdose [22].

Conclusion

The debate concerning digoxin use continues Rathore et al. [25], discussed the benefit of digoxin in that it reduces hospitalization with heart failure and depresses ventricular function; however, it may not prevent mortality [25]. CHF statistics is alarming and the need for effective treatment is inevitable, the Framinigham study shed light on the incidence, prevalence, and prognosis of CHF and the therapies administered was not effective. The question of administering digoxin as a treatment for heart failure continued, although, specific guidelines regarding the use of digoxin in treating heart failure was established [27].

The economic impact of heart failure is significant based on hospitalization and patients' quality of life after diagnosis of heart failure [6]. Hospitalization with CHF is greater than 900,000 yearly with readmission rate of 20%, however, effective therapies have not been established, as digoxin continues to be the most common therapy currently used [26]. The recommended treatment for heart failure includes digoxin, beta blockers, angiotensin-converting enzyme inhibitor, calcium channel blockers, and diuretics for which digoxin has been proven effective along with other treatment for various comorbidities associated with heart failure.Many researchers have supported the effectiveness of digoxin and reassures that its low doses are safe and important for the improvement of symptoms of heart failure. It is also suggested that there is a need to optimize current therapies and improve strategies for selecting therapy [11].

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