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REVIEW

Digoxin intoxication

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ABSTRACT
Digoxin was first isolated from Digitalis lanata in 1930. Digoxin is a cardiac glycoside used in the treatment of heart failure and arrhythmia. It was approved in 1998 by the American Food and Drug Administration for the treatment of heart failure. Although it is frequently used in heart failure patients, it can be used for atrial fibrillation and heart palpitations. It can be used orally or by intravenous injection. It exerts its effects by inhibiting the Na^+, K^+-dependent ATPase pump in cardiac cells. It slows heart rates by its negative effect on the sinoatrial node. It has a positive effect on ventricular contraction. However, it causes a decrease in heart rates due to its negative effect on the atrioventricular node. The narrow safety margin of blood digoxin levels raises some concerns about the drug. Toxic effects can be seen if serum levels rise above 2 ng/mL. Common effects include breast enlargement in men, loss of appetite, confusion, deterioration in visual quality, and disturbances in heart rhythm. Our aim in this article is to summarize the effects of digoxin on the cardiovascular system and current approaches in case of possible side effects.

Keywords: digoxin, heart failure, pharmacokinetic profile

ÖZET
Digoksin zehirlenmesi
Digoksin ilk kez 1930 yılında Digitalis lanata isimli yüksük otundan izole edilmiştir. Digoksin, kalp yetmezliği ve ritm bozukluğu tedavisinde kullanılan kardiyak bir glikoziddir. Kalp yetmezliği tedavisinde Amerikan Gıda ve İlaç Dairesi tarafından 1998 yılında onaylanmıştır. Kalp yetmezliği hastalarında sıklıkla kullanılmasına rağmen atriyal fibrilasyon ve kalp çarpıntısı için kullanılabilmektedir. Oral ya da damar enjeksiyonu yoluyla kullanımı mümkündür. Etkilerini kardiyak hücrelerdeki Na^+, K^+'a bağlı ATPaz pompasını inhibe ederek gösterir. Sinoatriyal düğüm üzerine negatif etkisiyle kalp hızlarını yavaşlatır. Buna rağmen ventrikül kontraksiyonunu olumlu etkilemektedir. Fakat, atriyoventriküler düğüm üzerindeki negatif etkisinden dolayı kalp hızlarında azalmaya neden olur. Kan digoksin düzeyinin güvenlik aralığı dar olması ilaç hakkında bazı endişelere neden olmaktadır. Serum düzeyleri 2 ng/mL'nin üzerine çıkması durumunda toksik etkiler görülebilmektedir. Yaygın etkiler arasında erkeklerde meme büyümesi, iştahsızlık, konfüzyon, görme kalitesinde bozulma ve kalp ritminde bozulmalar gibi etkiler mevcuttur. Bu yazımızdaki amacımız, digoksinin kardiyovasküler sistem üzerine etkilerini ve olası yan etkileri durumunda güncel yaklaşımları özetlemektir.

Anahtar kelimeler: digoksin, kalp yetmezliği, farmakokinetik profil

INTRODUCTION

Digoxin has been used in the treatment of several disorders for centuries; however, it was firstly used in cardiac diseases in England in1785 with the discovery of its effects on the heart by William Withering [1]. Digoxin is classified as a cardiac glycoside. Digitoxin and ouabain are other members of the cardiac glycoside family and are rarely used compared to digoxin. Digoxin is derived from Digitalis purpurea and Digitalis lanata, which are commonly known as the foxgloves, and is currently used in the treatment of heart failure and arrhythmias [2]. Despite the discovery of novel therapeutic agents with advanced technology, digoxin is still the most preferred treatment in heart failure due to its inexpensive and well-tolerated feature [3]. Digoxin is one of the most commonly prescribed medications worldwide [4].

The incidence and prevalence of heart failure increases with age. Due to the high prevalence of heart failure in the elderly patient population, digoxin is widely used for the treatment. Despite its advantages of being widely used, factors including a decrease in the body mass index and renal function, an increased incidence of concomitant disorders and an increase in the number of medications with age, and narrow therapeutic and toxic dose ranges of digoxin are associated with an increased risk of intoxication. Intoxication generally occurs due to chronic use of digoxin. Acute digitalis intoxication is rather uncommon [5]. Increased level of serum digoxin over the therapeutic limit is associated with increased mortality [6]. In several case series, mortality rates in digoxin intoxication have been reported between 20% and 30% [7-9].

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MECHANISM OF ACTION

The major mechanism of action of digoxin begins after blocking the alpha subunit by binding to the sodium-potassium ATPase pump located on the cell membrane. Intracellular calcium increases as a result of the decrease in sodium-calcium exchange due to an increase in intracellular sodium [10,11]. Tension of the actin and myosin filaments in cardiac sarcomeres is increased as a result of the increase in intracellular calcium. These changes lead to an increase in cardiac contractility by using digoxin in therapeutic doses. In addition to these effects, digoxin also has neurohormonal effects. Digoxin leads to an increase in heart rate variability, a decrease in plasma renin activity, and an inhibition in the sympathetic system in patients with heart failure. Digoxin has a direct inhibitory effect on the sympathetic system; its parasympathomimetic effects have also been demonstrated [11-13]. In addition, digoxin causes an increase in baroreceptor sensitivity [14]. The effects of digoxin on brain natriuretic peptide and cytokines, such as tumor necrosis factor-alpha, have also been demonstrated in recent studies [15,16].

Digoxin-related electrophysiological changes are associated with the inhibitory effect of digoxin on the sodium pump in the cell membrane and its effects on the autonomic system. Consequently, deceleration in the sinus rate, prolongation of the refractory period in the atrioventricular (AV) node, and slowing in conduction occur. Digoxin does not have a significant effect on Purkinje fibers at therapeutic doses. Due to an increase in these changes at toxic doses, digoxin leads to complete AV block and ventricular arrhythmias related to the increase in spontaneous conduction in Purkinje fibers [17].

PHARMACOLOGIC EFFECTS

Digoxin is absorbed from the gastrointestinal tract in a proportion of between 60% and 80%. Approximately 30% of the digoxin is bound to plasma albumin. Most of the digoxin is excreted from the kidneys by glomerular filtration and the tubulus by secretion without changing [18]. In addition to cardiac muscle, digoxin also binds to skeletal muscle. Therefore, serum digoxin and tissue levels are not the same. In general, the therapeutic dose range is considered to be 0.5-1.5 ng/mL [19]. The most effective dose range in the treatment of chronic heart failure has been reported to be 0.5-0.9 ng/mL [20, 21]. Without a loading dose, digoxin reaches to a stable serum level in 6-7 days in a patient with normal renal function. Digoxin can also be used intravenously. Intravenous administration of digoxin at high doses causes peripheral vasoconstriction [22]. Digoxin mechanism of action is shown in Figure 1.

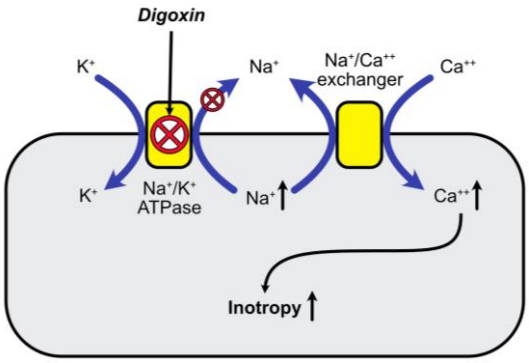

Figure 1. Mechanism of action of digoxin at the cellular level.

DIAGNOSIS IN DIGOXIN INTOXICATION

Drug intoxication is an important problem in elderly patients. The most frequent reasons of intoxication in the elderly population include dementia, unconsciousness, inappropriate drug usage, and drug storage conditions. Moreover, a high dose of drug ingestion for suicidal purposes can also cause intoxication. Digoxin intoxication is one of the most frequent causes of emergency service admissions due to drug intoxication. In the study of Digitalis Investigation Group related to digoxin use, the hospitalization rate due to digoxin intoxication was 2% [23,24].

Digoxin intoxication generally occurs as a result of using high doses to obtain high therapeutic efficacy [25]. It is often observed in elderly patients with heart failure and reduced renal function. Diagnosis of digoxin intoxication is based on clinical suspicion. Serum digoxin levels >2.0 ng/mL is an important risk indicator for intoxication. Measuring the serum level of digoxin only assists to obtain an accurate diagnosis. There is no definite relation between the serum level of digoxin and the clinical presentation, since the serum digoxin concentration is not dose-dependent only; it is closely associated with present clinical status of the patient and other concomitant medications. Diuretics, anti-arrhythmics (amiodarone, verapamil, and propafenone), macrolide antibiotics, and antacids that are used with digoxin can lead to intoxication by increasing the serum digoxin level.

The clinical manifestations of digoxin intoxication occur in various forms. Specifically, the clinical manifestations may present with gastrointestinal system symptoms, including nausea, vomiting, diarrhea, and abdominal pain, or as central nervous system symptoms, such as weakness, headache, confusion, apathy, and vision disturbances (blurred vision, yellow-green chromatopsia, yellow halo, and photopsia [26].

The electrocardiographic findings may present in various forms. There is not always a single type of dys-rhythmia. Premature ventricular beats, paroxysmal atrial tachycardia, AV block, nodal rhythms, and bidi-rectional

ventricular tachycardia are often noted on the electrocardiography (ECG). However, these ECG findings are not specific. Most of the patients admitted to the hospital with a preliminary diagnosis of digoxin intoxication are elderly individuals. Conduction disorders or arrhythmias secondary to coronary ischemia independent to digoxin may also be observed in this pa-

tient group as a consequence of advanced age. Since these types of arrhythmias resemble the arrhythmias which occur with digoxin intoxication, these conditions should also be considered when digoxin intoxication is suspected.

There are some conditions which increase the sensitivity to digoxin intoxication. Indeed, intoxication symptoms may be present even though serum digoxin levels are normal. The following conditions should therefore be considered in patients suspected with digoxin intoxication: renal failure, some concomitant medications, electrolyte imbalances (hypomagnesemia, hypercalcemia, and particularly hypokalemia), low body mass index, chronic hypoxia, alkalosis, hypothyroidism, cardiac amyloidosis, acute coronary syndromes, and digoxin hypersensitivity [27].

The mortality rate of acute digitalis intoxication varies in different case series, but is generally 5% to 10% [28]. The mortality rate is increased by advance age and renal failure.

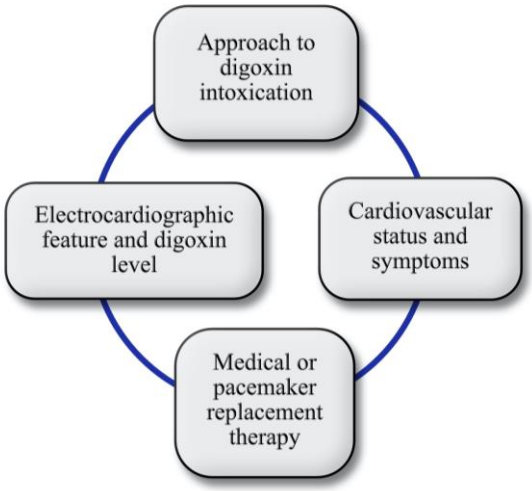

Figure 2. General approach algorithm for digoxin intoxication.

MANAGEMENT OF DIGOXIN INTOXICATION

The most important issues in the diagnosis of digoxin intoxication are suspicion and early diagnosis. When digoxin intoxication is suspected, digoxin should be discontinued firstly, and if any other medications are present which may increase the serum digoxin level should be immediately discontinued. The patient should instantly be monitored in terms of hemodynamics. The medical histories should be obtained from patients or their relatives during emergency admissions. The digoxin dose and usage, as well as the name of the other concomitant medications and existing diseases are important in the diagnosis, follow-up, and treatment of digoxin intoxication. In addition to measurement of the serum digoxin level, serum electrolyte level, renal function, and ECG should be evaluated. If the time since the last digoxin dose is <30 minutes, vomiting should be induced or gastric lavage is recommended. Patients do not benefit from hemodialysis for digoxin intoxication due to the large volume of distribution of the drug [19].

Following all of these evaluations, electrolyte imbalances, such as hypomagnesemia, hypercalcemia, and hypokalemia should be corrected. It is especially important to focus on hypokalemia. If there is profound hypokalemia, attempts should be performed for immediate replacement therapy. The presence of AV block on ECG or renal function should be assessed before this replacement therapy. The visual for the approach to digoxin intoxication is shown in Figure 2.

In the presence of AV block or symptomatic bradycardia according to monitoring and ECG findings, a transient cardiac pacemaker should be immediately placed in the case of an inadequate response to an initial trial of intravenous atropine. Hemodynamic monitoring and follow-up is sufficient in other asymptomatic and hemodynamically stable patient groups.

In cases involving severe life-threatening digitalis intoxication, digoxin Fab antibodies should be used [29]. Due to these antibodies, digoxin and digoxin Fab antibodies form immune complexes, which are excreted via the renal pathway. The duration of this antibody treatment is prolonged in the presence of renal failure. Measurement of the serum digoxin level after this process will not provide accurate results due to these complexes. Digoxin Fab antibody treatment, which is the most effective treatment method of digoxin intoxication alone, is very important [30].

APPROPRIATE DOSING IN DIGOXIN TREATMENT

Serum digoxin levels of 0.5-1.0 ng/mL can be achieved by daily doses of 0.25-0.5 mg in most patients with heart failure. The appropriate therapeutic dose range is between 0.5 and 2.0 ng/mL. Age, gender, renal function, diuretic usage, concomitant medications, and the use of other drugs that are known to affect the serum digoxin level should all be considered when determining the digoxin dose. In a male patient in whom heart failure is stable, the serum digoxin level can be maintained <1.0 ng/mL with a 0.25 mg/day dose. If the patient is elderly and has a mild reduction of renal function, a daily dose of 0.125 mg is sufficient in females [31]. If initiation of digoxin treatment is considered in patients under chronic heart failure treatment, there is no need for a loading dose. A loading dose may be necessary in emergency conditions. The loading dose may be between 0.5 and 0.75 mg in patients with normal renal function.

MEASUREMENT OF THE SERUM DIGOXIN LEVEL

The serum digoxin level should be measured in patients having high risk for digoxin intoxication. It should be considered that serum digoxin has an extensive volume of distribution. Thus, problems occur in measurement standards. For example, since serum digoxin levels may decrease following physical activity, the serum digoxin level should be measured by obtaining blood samples after at least 2 hours of resting in the supine position if possible [32, 33].

Stable serum levels are achieved 6-7 days after the initiation of digoxin treatment. Therefore, it is more appropriate to measure the digoxin level at least 1 week after the initiation of the treatment. The half-life of digoxin is 36-48 hours in patients with normal renal function. The half-life of digoxin is prolonged to 4-7 days in the case of decreased renal function [11]. When measuring the digoxin level, the time since the last dose of digoxin is important. Measurement can be performed at least 6-8 hours after the ingestion of the last dose; however, the serum level should be optimally measured just prior to the next scheduled dose [34]. If the measured serum level is within the preferred range, re-measurement is not necessary unless there is renal dysfunction, a change in clinical status, significant weight loss, or an initiation of a new medication which might increase the serum digoxin level [31].

DISCUSSION

Despite advances in drug technology, digoxin is one of the most commonly prescribed drugs worldwide for the treatment of heart failure owing to its low cost and easy tolerability. Frequent use is associated with an increased incidence of intoxication. Clinical status, age, renal function, and concomitant medications should be considered before prescribing digoxin. It is important to follow-up carefully the clinical symptoms of the patients having digoxin treatment and accordingly to modify the treatment. Digoxin can be used more safely when all these factors are taken into consideration. Currently, it appears that digoxin will continue to be used for a long period of time.

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