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Education Article

Cardiotoxicity of Doxorubicin: Causes, Diagnosis, Consequences and Possibilities of Prevention

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SUMMARY

Introduction: Doxorubicin is an antibiotic from the anthracycline group, with clinical use limited by adverse reactions, primarily cardiotoxicity.
Material and Methods: This article provides an overview of therapeutic and toxic doses of doxorubicin, the mechanism of side effects, markers for early detection as well as currently available preparations for preventing its toxicity. We searched PubMed, Google Scholar, SCIndex, Dimension, Scopus and Google for English and Serbian language abstracts, using the searching terms „doxorubicin", „cardiotoxicty", „carotenoids", „oncology", „oxidative stress", „DNA damage" and „biomarkers".
Topic: The mechanism of side effects is still unclear and is considered to be multifactorial including ROS overproduction, reducing levels of endogenous antioxidants, DNA damage, large drug accumulation in cardiac tissue, calcium overload, histamine release, and impairment of autoimmune regulation of cardiac function Manifestations of cardiotoxicity are mainly acute (appear inside 24^{h} atypical changes of ST segment, decrease in QRS complex voltage, tachycardia and supraventricular extrasystoles are observed, but can also be subacute and chronic (cardiomyocyte edema, disorganzation, fibroblast proliferation, necrosis). Diagnosis of cardiotoxicity is based on ECG, ECHO, and biochemical markers, among which the most important are troponins, while pathohistological verification is necessary for the final diagnosis. Some medications (carvedilol, atorvastatin) have showed some level of cardioprotection against DOX, but there is no overall agreement on their administration solely for this purpose. An increasing number of studies have tested various dietary supplements and natural preparations (already in the human diet) in order to

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discover those that could completely prevent or reduce the toxic effects of doxorubicin, with special focus on carotenoids.
Conclusion: Cardiotoxicity is the leading side effect of doxorubicin, and therefore there is an active search for either new biomarkers and/or diagnostic protocols that would detect toxicity in time, as well as substances able to prevent the occurrence or alleviate DOX-induced cardiotoxicity.

Keywords: Doxorubicin, Cardiotoxicity, Oncology, Side Effects

INTRODUCTION

Doxorubicin, also known as adriamycin, is an antibiotic from the anthracycline group, first isolated from the bacterium Streptomyces peacetius, while today it can also be chemically synthesized. Data from the World Health Organization (WHO) classify it as one of the drugs necessary for the treatment of the 10 most common types of cancer. It is primarily used in the treatment of endometrial, ovarian, breast, testicular and lung cancers. However, what limits the clinical use of this drug the most is its main side effect - cardiotoxicity. The occurrence of fatal cardiotoxicity in both pediatric and adult patients is characterized by irreversible cardiomyopathy [1,2,3]. It is estimated that about 11% of patients with doxorubicin-treated cancers develop acute cardiotoxicity. In addition to the heart, other organs can also be affected by this therapy, primarily the kidneys, liver and brain [3,4]. Women are more susceptible to the development of side effect of doxorubicin compared to men, in terms of increased suppression of cardiac contractility and a higher chance of developing subclinical cardiotoxicity. In addition to gender, age can also be a risk factor - people under 25, as well as those over 75 are more susceptible to cardiotoxicity. Concomitant use of another cardiotoxic drug, simultaneous mediastinal radiotherapy and high doses of doxorubicin may also increase the risk of its side effects. In order to reduce the effect of doxorubicin-induced cardiotoxicity, the use of many drugs as well as various herbal substances have been studied, among which carotenoids have been the most tested [4]. However, most oncology patients receiving doxorubicin have less serious side effects, including gastrointestinal problems, hair loss and inflammation of the oral mucosa [1].

MATERIAL AND METHODS

This article provides an overview of therapeutic and toxic doses of doxorubicin, the mechanism of side effects, markers for early detection as well as currently available preparations for preventing its toxicity. We searched PubMed, Google Scholar, SCIndex, Dimension, Scopus and Google for English and Serbian language abstracts, using the searching terms „doxorubicin", „cardiotoxicty", „carotenoids", „oncology", „oxidative stress", „DNA damage" and „biomarkers".

Based on expert selection review, we chose both open and blinded studies, reviews and meta analysis, and available comments and editorials, related to the MESH terms.

TOPIC

Doses, method of administration, time of occurrence and mechanism of side effects

Doxorubicin (DOX) is administered intravenously (i.v.), dissolved in 0.9% NaCl solution or 5% glucose solution, for 3 to 10 minutes to reduce the risk of thrombosis or perivenous extravasation. The therapy dose is calculated based on body surface area, and the total dose per cycle may vary depending on the specific treatment regimen. When used as monotherapy, 60-75 mg/m^2 is recommended, and it can be given as a single dose or divided into 3 consecutive days or divided into the first and eighth day of the cycle. Each subsequent cycle is repeated every 3 to 4 weeks. If given in combination with other antitumor drugs, the dose is reduced to 30-60 mg/m^2 every 3 weeks. Toxic doses of doxorubicin differ due to individual characteristics of the organism as well as other factors, including interaction with other drugs. In a study conducted by Lee and Hill, cardiotoxicity in adults was caused by doses of 400 to 700 mg/m^2, while in children it was a dose of 300 mg/m^2 [5]. Further research has shown that toxic doses generally range from 8 to 400 mg/m^2, up to a maximum cumulative dose of 500 mg/m^2 [6]. In animals, damage is

caused by a single doses in the range of 0.1--10 mg/m^2 to the highest cumulative doses of 12-20 mg/m^2. Where the dose of 20 mg/m^2 in animals is equivalent to the dose of 900 mg/m^2 in humans [7,8,9]. The clinical use of doxorubicin is limited by adverse reactions, primarily cardiotoxicity. The time of onset of side effects is very variable and difficult to predict in both humans and animals. According to the time of onset, they are divided into acute, which can occur after only one dose, subacute and chronic, which occur after prolonged use of this drug [7,9]. Cardiotoxicity can occur either as acute, mostly asymptomatic, or chronic, leading to irreversible changes in the heart [10].

The mechanism of side effects

The mechanism of side effects is still unclear and considered to be multifactorial. In the first place, doxorubicin can be converted to an intermediate metabolite, which due to instability is converted back to doxrubicin, producing free radicals (reactive oxygen species, ROS) thereat. Increased ROS production can be neutralized to some extent by antioxidant defense mechanisms of the cell, but if ROS production exceeds the capacity of antioxidant defense it leads to a condition known as oxidative stress (OS) Doxorubicin stimulates the development of OS, both by increasing the production of ROS and by reducing antioxidant mechanisms. ROS in the cell damages various cellular organelles and structures, of which the most important for the fate of the cell itself, as well as the function of the entire organ, is the damage to mitochondria, cell membranes and DNA. Mitochondria are among the key intracellular sites where ROS production occurs, and this mechanism of action of doxorubicin can be partly explained by the fact that heart cells are richer in mitochondria than other tissues and consequently produce much higher amounts of ROS [11,12]. The mechanism of damage to the cell membrane and other membranes inside the cell is lipid peroxidation, as a result of which malonyl aldehyde (MDA) accumulates in the cell/tissue. DNA damage occurs simultaneously with mitochondrial and later cell membrane rupture, ultimately resulting in cardiomyocyte apoptosis. Another mechanism is that DOX significantly reduces the levels of endogenous antioxidants, which affects the capacity of anti-oxidative defense of the organism/cell [13]. According to the nature and mode of action, all antioxidants in the body can be divided into enzymatic and non-enzymatic. Enzymes involved in the defense against oxidative stress are a) superoxide dismutase (SOD): catalyzes the removal of superoxide anion radicals, producing hydrogen peroxide and molecular oxygen. It is present in the cytosol and mitochondria of all tissues in the body; b) catalase (CAT): its antioxidant activity is based on the removal of toxic hydrogen peroxide. It is present in the mitochondria of all tissues; c) Glutathione peroxidase (GSH-Px): catalyzes the reduction reaction of hydrogen peroxide or organic peroxides to water molecules in the presence of reduced glutathione as an electron donor; d) Glutathione reductase (GSH-R) - catalyzes the reduction of oxidized glutathione (GSSG) to reduced glutathione (GSH), maintaining an adequate concentration of reduced glutathione in the cell. On the other hand, the most important non-enzymatic mechanism of antioxidant protection is the tripeptide glutathione (GSH; γ-glutamyl-L-cysteinyl glycine). GSH protects the body from free radicals by neutralizing or reducing them [14]. Oxidative stress caused by the use of doxorubicin in the cardiovascular system affects the onset and development of atherosclerosis, hypertension, coronary heart disease and myocardial infarction [15]. The next mechanism begins with the entry of the drug into the nucleus of the target cell, where it is incorporated into the DNA of the host and binds to topoisomerase II. Topoisomerase II has a role in DNA repair and repair of its chains. Doxorubicin inhibits the process of DNA repair and leads to a large number of double-stranded breaks. The presence of these interruptions leads to the initiation of the apoptosis process [4]. Other mechanisms could be significant drug accumulation in cardiac tissue, calcium overload, histamine release, and impairment of autoimmune regulation of cardiac function [9,10,16].

Cardiac and biochemical verification of doxorubicin-induced damage

Acute cardiotoxicity occurs only a few hours after intravenous administration and may persist for up to several days. Initial changes, can be detected in the first 24 hours after drug administration with the help of electrocardiography (ECG) when atypical changes of ST segment, decrease in QRS complex voltage,

tachycardia and supraventricular extrasystoles are observed. In most patients, the changes are asymptomatic and usually resolve spontaneously. However, in some, the changes persist, and if they are not detected, and doxorubicin therapy is continued, irreversible changes occur that lead to heart failure and death [17]. In addition to the ECG, echocardiography (ECHO), nuclear imaging and myocardial biopsy have been used to monitor the condition of patients after the first dose of doxorubicin. ECHO parameters were the thickness of the intraventricular septum and posterior wall of the left ventricle (LV) in diastole and systole, internal diameter LK, fractional shortening of the short axis LK, end-diastolic and systolic volume LK, stroke volume and ejection fraction left ejection fraction - LVEF). The same study in rats monitored heart rate and arterial blood pressure (ABP). The obtained results show that there was an increase in heart rate and increased BP in the doxorubicin-treated groups [18]. These changes are mostly registered with the development of the first symptoms, when the damage to the heart function is already in an advanced stage, and the chances of survival are very low. Therefore, monitoring various biochemical markers is of utmost significance, as well as other diagnostic methods that would be carried out preventively in all patients in order to detect early the first subclinical changes that would indicate cardiotoxicity [19]. Biochemical markers that can be used to detect changes in the heart are lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), creatine kinase (CK) and cardiac creatine kinase. CK-MB). Some studies in which these parameters were monitored showed an increase in the period from 3 to 24 hours after the onset of acute toxicity [20]. Also, proinflammatory cytokines, primarily TNF-alpha (tumor necrotic factor alpha) and interleukin 6 (IL-6) [21,22], increase in heart damage. Levels of MDA, SOD, CAT, GPx, GSH as well as total antioxidant capacity (TAC) can be measured to monitor oxidative stress [23]. MDA blood level can be measured in both humans and animals, while the activity of antioxidant enzymes is mainly analyzed from tissues, which makes it difficult to apply this method in the human population. In the last few years, BNP (brain natriuretic peptide) and cardiac troponins (cTns) have been used as indicators of damage/dysfunction [19]. Previous research indicates that measuring cTns detects cardiotoxicity early, long before the first left ventricular functional disorders observed on ECHO. The peak increase in cTn blood level is between 4-6 hours after administration, with a gradual decrease until the end of 24 hours. Doxorubicin-induced cardiotoxicity is associated with prolonged elevated cTns levels and its values correlate with cumulative doses of doxorubicin [24]. The disadvantage of diagnostics using biochemical markers is that the time of their increase is not always precisely defined. Also, they are not specific for only one disease, but can indicate damage of different etiology. Therefore, there is a need to determine other parameters that would determine the toxicity caused by doxorubicin more accurately or at least to form protocols that would combine existing methods in a way that would indicate with greater certainty that the damage is due to doxorubicin.

Histological verification of doxorubicin-induced damage

In addition to all the above diagnostic methods, histopathological confirmation is necessary for an accurate diagnosis. Cardiac biopsies are not performed routinely, both in cases of suspected acute and in cases of suspected chronic cardiotoxicity. Samples are mostly obtained after autopsies of patients, or after experimental research on animal models. Changes in histopathological tissue analysis are predominantly found in the left ventricular wall and septum. Saad et al. were the first to define a method for diagnosing cardiomyopathy caused by doxorubicin, taking into account these changes if they are seen in three or more visual fields (Table 1, Figure 1). Cardiomyopathy is considered serious if the total score of the preparation is 3 or more points, moderate 2 points, while 1 point represents bad cardiomyopathy [9]. Other authors have also observed cytoplasmic vacuolation, infiltration of leukocytes and eosinophils, hemorrhage, pyknotic nucleus of cardiomyocytes, disruption of distribution or loss of myofibrils [8]. These criteria can be assessed on standard hematoxylin - eosin staining (HE), thus the whole histological assessment is accessible and easy to perform. In addition, Masson's trichrome and terminal deoxynucleotide transferase (TUNEL) are used [25]. If necessary, immunohistochemical staining, such as anti -

Rating	Change
+1	Cardiomyocyte edema and interstitial edema
+1	Disorganization of cardiomyocytes/microfilaments with or without fibroblast proliferation
+1	Myocytolysis/cardiomyocyte necrosis
0	No damage

Table 1. Evaluation of changes in pathohistological tissue analysis [9]

p53, anti - TNFα, can be used to monitor more specific changes. As a final result, the detected changes lead to dilatation of the heart, which leads to a decrease in its weight, which can also be one of the parameters for the diagnosis of toxic effects [7].

Medications, substances and natural plant extracts with potential cardioprotective features

An increasing number of studies are dealing with/testing/investigating various substances that could completely prevent or reduce the toxic effects of doxorubicin. Numerous drugs that have already been registered and used in the treatment of other diseases are tested in pursuit of dox-cardiotoxcity prevention. Better systolic and diastolic heart function was observed in patients who used carvedilol (beta blocker) for 6 months. Also, the incidence of death and heart dysfunction decreased. The mechanism of its action has not yet been fully elucidated. It has been found to reduce the concentration of ROS, which indicates its antioxidant effect. Also, one of the studies proved that carvedilol prevents mitochondrial dysfunction by this mechanism. There are indications that other beta-blockers may have the same effect, however, this hypothesis has not yet been confirmed [26]. Statins reduce vascular inflammation and oxidative stress, and thus contribute to the improvement of heart function. They reduce the production of cardiac nitrotyrosine and inflammatory responses, and on the other hand, they accelerate the anti-apoptosis mechanisms. In the conducted research, they influenced the increased production of SOD in order to prevent the production of reactive oxygen. Another study suggested that atorvastatin may be effective in maintaining LVEF in patients treated with anthracyclines [11]. Silymarin, a drug used in the treatment of liver disease, is also mentioned as another protective agent. Research indicates that it reacts at the level of the cell membrane, increasing its resistance to harmful influences,

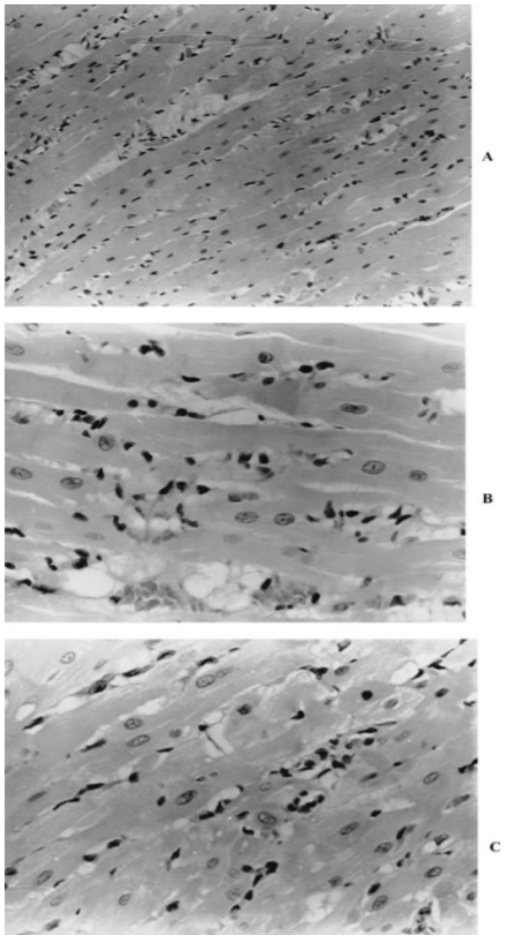

Figure 1.

A) Severe interstitial edema, mononuclear cell infiltration, cardiomyocyte swelling and disorganization with perinuclear vacuolation, HE, 200x;
B) Cardiomyocyte swelling with disorganization and extensive focal necrosis, HE, 400x;
C) Cardiomyocyte swelling with necrosis and perinuclear vacuolation, HE, 400x [9].

probably changing its physico-chemical properties. It also interacts with ROS and converts them into less reactive and toxic compounds. Its benefits have also been proven in a study on rats conducted by Rašković et al. The activity of antioxidant enzymes was monitored, which significantly increased after the application of doxorubicin. The obtained results indicate a reduction of oxidative stress in treated animals. These changes are accompanied by an appropriate pathohistological finding. Significant hyperemia was observed in groups treated with doxorubicin alone, while in groups where a combination of doxorubicin and silymarin was used, this tissue response was absent, proving the protective role of silymarin [27].

Also, the research included dietary supplements and natural preparations that are already in the human diet [28]. Recently, the center of interest has been the action and possibilities of carotenoids in many fields. Some of them, called provitamin A carotenoids, can be converted into vitamin A, which has a strong antioxidant capacity. In this way, they participate in the regulation of vision, and their lack can lead to various eye diseases. In addition, they are associated with potential influences on reproduction, embryogenesis, immune system, intracellular connections, and metabolic pathways [29]. Trans forms of beta carotene act to increase HDL levels, and thus have a protective effect in the process of atherosclerosis. Other carotenoids reduce the incidence of acute myocardial infarction as well as other heart diseases [30]. Studies indicate a protective role of carotenoids in doxorubicin-induced toxicity. Carotenoids are thought to reduce lipid peroxidation in the heart, meninges, liver and kidneys. The protective effect correlates with the ability to remove oxygen free radicals (ROS). The protective effect was proven histopathologically, and there was no increase in biochemical markers of damage in these organs [21,22]. Research in mice shows that the use of carotenoids in tumor tissue did not reduce oxidative damage (lipid peroxidation and increase in malonyldehyde levels) nor did it significantly reduce antioxidant levels. In this way, they reduced the size of the tumor. The same study proved that the use of carotenoids prevented doxorubicin-induced damage to healthy (tumor-unaffected) organs without interfering with the antitumor effect of doxorubicin [31]. It is assumed that various mechanisms can prevent the development of malignant tumors, primarily ovarian, breast and prostate. Increasing number of research is focused on examining the possible use of carotenoids in the treatment of malignancy. Dexrazoxane is a cardioprotective agent for anthracycline-induced cardiotoxicity. It interferes with the production of ROS mediated by Fe ions, blocks the inactivation of respiratory enzymes by iron complexes and thus reduces the toxic effect of doxorubicin on the heart. Omega 3 fatty acids are found in fish and certain plants, reducing the sensitivity of cardiomyocytes to oxidative stress. This happens through the combination of several mechanisms, which are strengthening the antioxidant defense, changing the fluidity of the membrane and preventing the release of intracellular calcium under the action of oxidative stress. Coenzyme Q10 is a liposoluble substance located in the mitochondria of all aerobic respiratory eukaryotic cells. By reacting directly with free radicals or regenerating tocopherols and ascorbates from the oxidative state, it provides effective protection against anthracycline-inducing toxicity [11]. Curcumin active element of turmeric and carvacrol, the main phenol compound, are used as new agents in the treatment of heart failure. It has been suggested that they may inhibit cardiomyocyte hypertrophic responses [32]. In recent years, extensive research has been conducted on small molecules that target mitochondria and prevent excessive ROS production. These molecules are classified into three groups (natural, semi-synthetic and synthetic), and one of the advantages is that they do not reduce the effect of doxorubicin [11]. Also, the effect of celery juice on doxorubicin-treated animals was investigated. In the groups that drank celery leaf juice, there was a decrease in lipid peroxidation, which is one of the markers of oxidative stress, while celery root juice did not show this effect [33].

CONCLUSION

Cardiotoxicity is the leading adverse event of doxorubicin, resulting in termination of therapy or subsequent long-term impairment of cardiac function. The main focus in eliminating both acute and chronic cardiotoxicity is finding new biomarkers and / or developing new, more comprehensive diagnostic protocols that will detect toxicity in time and thus prevent its progression. On the other hand, we are actively looking for already registered drugs or substances of other origin, primarily herbal, that would be used for the purpose of preventing the occurrence or alleviation of cardiotoxicity.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Kardiotoksičnost doksorubicina: uzroci, dijagnostika, posledice i mogućnosti prevencije

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KRATAK SADRŽAJ

Uvod: Doksorubicin je antibiotik iz grupe antraciklina, čija je klinička upotreba ograničena neželjenim dejstvima, pre svega kardiotoksičnošću.
Materijal i metode: Ovaj rad daje pregled terapijskih i toksičnih doza doksorubicina, mehanizama nastanka neželjenih efekata, markera za rano otkrivanje kao i trenutno dostupnih preparata za prevenciju njegove toksičnosti. Pretražene su baze podataka PubMed, Google Scholar, SCIndex, Dimension, Scopus i Google, koristeći pojmove za pretragu: *doxorubicin*, *cardiotoxicty*, *carotenoids*, *oncology*, *oxidative stress*, *DNA damage* i *biomarkers*.
Tema: Mehanizam nastanka neželjenih efekata još uvek je nerazjašnjen i smatra se da je multifaktorijalan, te da uključuje pojačanu produkciju kiseoničnih radikala, supresiju aktivnosti endogenih antioksidanasa, oštećenje DNK, akumulaciju leka u kardiomiocitima, poremećaj metabolizma kalcijuma, oslobađanje histamina i narušavanje autoimune regulacije srčanog mišića. Manifestacije kardiotoksičnosti su mahom akutne (unutar 24^{h}, promene ST segmenta i QRS kompleksa, tahikardija, i supraventrikularne ekstrasistole) ali mogu biti i hronične (edem i dezorganizacija kardiomiocita, nekroza i proliferacija fibroblasta). Dijagnoza kardiotoksičnosti se bazira na EKG i EHO nalazima, biohemijskim markerima (od kojh su najvažniji troponini) dok je patohistološka verifikacija potrebna za krajnju potvrdu. Pojedini lekovi (karvedilol, atorvastatin) pokazali su neki nivo kardioprotektivnosti kod primene doksorubicina, ali nema konsenzusa o njihovoj primeni isključivo u ove svrhe. Raste broj studija koje ispituju razne suplemente i prirodne produkte kako bi identifikovali one koji bi mogli u potpunosti sprečiti ili redukovati toksične efekete doksorubicina, a posebno se fokusiraju na jedinjenja iz grupe karotenoida.
Zaključak: Kardiotoksičnost je vodeće neželjeno dejstvo doksorubicina, te se stoga aktivno traga za novim biomarkerima i/ili dihagnostičkim protokolima koji bi na vreme otkrili toksičnost, kao i supstancama koje mogu da spreče pojavu ili ublaže kardiotoksičnost izazvanu doksorubicinom.

Ključne reči: doksorubicin, kardiotoksičnost, onkologija, neželjena dejstva

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