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REVIEW ARTICLE

Mechanism of Actions of Some Common Toxic Agents Causing Toxic Cardiomyopathy

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ABSTRACT

Background: Toxic cardiomyopathy is related to heart failure in many cases and may lead to death. We focused on the mechanisms by which some common toxic agents cause cardiomyopathy. We searched in articles, case reports, experimental and clinical studies on this topic

Our results have shown that the heart or the cardiovascular system is one of the most affected systems by toxic agents. We summarized studies which mentioned some common cause such as; "Anti-cancer drugs", "Anti-diabetic drugs", "Cocaine", "Ethanol", "Heavy Metals", and "Digitalis drugs" and their mechanism of action inducing cardiotoxicity. We concluded that mechanisms underlying toxic cardiomyopathy are complicated and variable. However, they generally include disruption of cell bioenergetics and intracellular calcium handling. It is also involved in: production of reactive oxygen species (ROS), development of oxidative stress and apoptosis induction. **Conclusions:** Toxic agents have a very harmful effect on the heart producing cardiomyopathy and heart failure. A lot of drugs and environmental toxins can produce cardiotoxicity including; anti-cancer drugs, anti-diabetic drugs, cocaine, ethanol, CO, and heavy metals their mechanisms of action are complicated and included many factors.

Keywords: Cardiomyopathy; Toxicity; Heart Failure; Toxic agent; Digitalis

INTRODUCTION

Cardiomyopathy is usually defined as any condition that causes primary ventricular or electrical cardiac dysfunction, that is not secondary to any other forms of cardiac dysfunction (Ex.: ischemia, volume-pressure overload, etc...) [1]. These conditions are frequently genetic [1], however, in some cases, cardiomyopathy can be caused by toxins. The true prevalence of toxin-induced cardiomyopathy is unknown. However, it is common in patients receiving chemotherapy [2]. In addition, a lot of diabetic patients receiving pharmacological therapy develops severe cardiovascular manifestations [3].

Therefore, the aim of this review article is to present the effect of these toxic agents on the heart and to explain the mechanism by which these toxins can cause cardiomyopathy and myocardial dysfunction. In this article, we will focus on: anti-cancer drugs, anti-diabetic drugs, cocaine, ethanol, carbon monoxide, various types of heavy metals, scorpion venom and finally the toxicity of digitalis drug and their mechanism of action.

Anticancer drugs

Cardiomyopathy is an adverse effect of anticancer drug therapy. Although the efficacy of anticancer treatments has improved, long-term outcomes are altered by the development of cardiotoxicity [4].

1-Anthracyclines:

Doxorubicin is a category of anti-neoplastic drugs extensively used in management of many malignancies. The mechanism of anthracycline-prompted cardiomyopathy has been studied, and of the many mechanisms proposed, free radical-mediated oxidative damage to the cardiac myocyte, with membrane lipid peroxidation and mitochondrial dysfunction have been suggested to be the most common mechanism [5].

2-Monoclonal antibodies:

Trastuzumab is a monoclonal antibody to human epidermal growth factor receptor type 2 [6].Trastuzumab and anthracyclines are suggested

to mediate cardiotoxicity via different pathways. The available lines of evidence suggest that trastuzumab can exacerbate the cardiotoxic effects of anthracyclines and thus, prior exposure to anthracyclines is regarded as one of the risk factors for trastuzumab-induced cardiotoxicity. Although it is generally believed that the trastuzumab-induced cardiotoxic effects are reversible, various preclinical studies have revealed its apoptotic effects on cardiomyocytes. Thus, the issue of the reversibility of its cardiotoxic effects remains to be fully resolved. The nature of trastuzumab-associated cardiotoxicity is exceedingly exceptional from that of doxorubicin and is called Type II CRCD which is related to myocyte disorder however now it is no longer associated with irreversible injury[7].

3-Cisplatin:

Cisplatin is one of the alkylating group of broad-spectrum antineoplastic drugs used against many types of tumors [8]. Cisplatin-induced cardiac disorder is associated with mitochondrial membrane depolarization together with ultrastructural abnormalities of the mitochondria. After cisplatin treatment. Cardio myocytes show signs and symptoms of apoptosis in the form of activation of the endoplasmic reticulum strain response, prolonged caspase 3 activity.

4-Arsenic trioxide:

Arsenic trioxide is an anticancer drug, inducing modifications in apoptotic signaling in most cancers cells. scientific reviews have proven that it is related to considerable cardiotoxicity. Exposure of H9C2 cardiomyocytes to clinically applicable concentrations of the drug (2–10 μM) showed apoptosis, ROS formation, intracellular calcium overload, and caspase-three activation [9].

5-Mitoxantrone:

Mitoxantrone is a DNA topoisomerase inhibitor and non-anthracycline antineoplastic agent. Cardiomyopathy is induced by long term use of mitoxantrone. In vitro and In vivo studies suggested the possible mechanism is alteration of ATP ranges with hyperpolarization of the mitochondrial membrane potential and changes of intracellular calcium. Another suggested mechanism is inhibition of ATP-synthase expression and with concomitant growth in ROS formation [10, 11].

Anti-diabetic Drugs

1-Sulphonylureas:

Sulphonylureas close ATP-dependent potassium channels, which are responsible for insulinotropic effect and the negative effects on the heart. It has been reported that sulfonylureas reduce blood flow of the myocardium during resting state which increase the risk for myocardial infarction [12].

2-Meglitinides:

Meglitinides stimulate insulin secretion. These compounds inhibit ATP-dependent potassium channels; however, because of the strong involvement of ATP-dependent potassium channels in the mechanism of action, caution should be present [13].

3-Glitazones:

Glitazones are a special category of anti-diabetic drugs including troglitazone, pioglitazone, and rosiglitazone which have slightly different chemical compositions and modes of action than the other categories. Chemically, they are chroman thiazolidinediones; some analogues are also available [14].

4-Oral hypoglycemic drugs

Biguanides, sulfonylureas, meglitinides, glitazones, and alpha-glucosidase inhibitors have been related to a variety of negative or even fatal cardiovascular events. Sulfonyleurea and meglitinides inhibit ATP dependent potassium channels while glitazones are chroman thiazolidinediones

The FDA recommended that to determine the effectiveness of a potential anti-diabetic medication for T2DM, the manufacturers demonstrate that the new drug would not result in an unreasonable increase in cardiovascular risk, as well as the fact that the study population contains patients who are at high risk. Other requirements included trials for at least two years. The gliflozins are currently being investigated for their long-term cardiovascular outcome [15].

Cocaine:

Cocaine is a sympathomimetic drug which has been used illegally as a stimulant and euphoric drug [16]. A lot of cases of cardiomyopathy in cocaine consumers have been reported [17].Cardiovascular effect of cocaine includes: vasoconstriction of the coronary blood vessels which causes ischemic heart diseases and myocardial infarction. It also causes generalized VC which causes hypertension and organs ischemia [18]. Effect of cocaine on the heart has different mechanisms. It Inhibits reuptake of norepinephrine and dopamine which increases sympathetic effect on the heart increasing its inotropic and chronotropic effects. It also inhibits the transient influx of sodium across the cell membrane leading to release of neurotransmitters which bind to alpha and beta adrenergic receptors leading to its stimulation which activates adenyl-

cyclase enzyme increasing cAMP which increases calcium influx into myocardial cells increasing force of contraction of myocytes. Elevated systolic calcium can cause sustained depolarization and trigger sustained action potential and extra-systole causing arrhythmias [18]. That may lead to left ventricular dilated cardiomyopathy [19].

Ethanol:

Alcohol or ethanol is the most toxic agent to be consumed all over the world. It was reported that up to 40% of patients with idiopathic dilated cardiomyopathy are alcohol consumers [20]. Alcohol has many different cardiac effects. They occur as a result of direct exposure of the cardiac tissue to alcohol or its toxic metabolites [21]. One of the most significant mechanisms of cardiac damage is mitochondrial dysfunction as it impairs the mitochondrial membrane decreasing the membrane potential, reducing the enzymatic activity and decreasing ATP synthesis. It also causes oxidative stress increasing ROS production leading to apoptosis [22]. As repair mechanisms; necrosis and excessive fibrosis follow apoptosis which decrease the capability of the myocardial contractility. It also causes disruption of calcium channels causing defects in sarcolemmal contractions. Ventricular hypertrophy and dilatation occur as compensatory mechanisms which will lead to heart failure [21].

Carbon monoxide:

Carbon monoxide (CO) is an odorless, colorless gas. It can cause organ damage and toxic effects even in small doses [23].

Several effects of CO on the cardiovascular system are well established such as myocardial infraction, arrhythmia, heart failure and pulmonary edema which are caused by ischemic hypoxia[24].

There are several proposed mechanisms to explain CO-induced cardiomyopathy:

(1) A classical explanation is that CO binds with haemoglobin forming carboxyhaemoglobin (COHb) and impairing oxygen delivery to mitochondria which causes hypoxemia and leads to systolic dysfunction. However, the explanation is contradicted by animal studies which shows increased sympathetic stimulation in CO-intoxicated animals leading to increased heart rate and maintained blood pressure [25].

(2) Myocardial stunning due to catecholamine surge caused by acute CO intoxication. [26] High levels of postmortem catecholamines were found in spinal and pericardial fluids in cases of CO poisoning. This is the most likely explanation for cardiomyopathy[26].

(3) Mitochondrial toxicity: CO causes inhibition of cytochrome c oxidase level at the mitochondrial chain, decrease of glutathione concentrations and of ATP generation [27].

(4) Toxic myocarditis due to high levels of CO: similar to what is seen in cases of severe scorpion envenomation [28].

Metals

Heavy metals, as cadmium, lead, mercury and arsenic, with multiple mechanisms (such as DNA damage and lipid peroxidation) can damage the cardiovascular system[29].

Cadmium (Cd):

Cadmium is a strong cardiotoxic heavy metal in the environment, which can be produced through chemical fertilizers, batteries and sewage [30]. Other studies have shown that cadmium toxicity is caused by cell apoptosis, DNA damage and oxidative stress. Cd toxicity can cause cardiotoxicity, hypertension and myocardial diseases such as atherosclerosis, hypertension, myocardial infarction and others. Cd poisoning increases antioxidant (glutathione, glutathione peroxidase, superoxide dismutase and catalase). It also decreases enzymatic activities of Cu,Zn-SOD [31].

Mercury (Hg):

Mercury toxicity was related to the CNS. However, increasing evidence suggests that methyl mercury exposure may increase the risk of adverse cardiovascular effects on populations . Hg-mediated vascular effects result in elevated oxidative stress, inflammation and decrease oxidative defense. Increased stress conditions and minimal protection this leads to thrombosis and mitochondrial dysfunction. Pathological findings related to mercury exposure and changes in lipid distribution included atherosclerosis, myocardial infarction and cardiovascular disease [31,32].

Lead (Pb):

Exosure to Pb can cause changes in systolic blood pressure, which can increase up to a factor of two in the range of 0.6 to 1.25 mm Hg. Pb exposure is associated with an increased incidence of clinical cardiovascular abnormalities such as coronary heart disease, stroke, peripheral arterial disease, left ventricular hypertrophy and changes in cardiac rhythm [33]. The contribution of Pb to cardiovascular diseases remains unclear

Digitalis Toxicity:

Digoxin is a well-known cardiac glycoside and one of the oldest drugs used today in cardiovascular disorder and its toxicity is very common due to narrow therapeutic index [34]. Digitalis normal mechanism of action includes: 1) inhibition of Na+/K+ ATPase increasing sodium

intracellularly. This increased Na is shifted extracellularly in exchange with calcium ions. Increased intracellular Ca+2 enhance myocardial contractility. 2) Increased intracellular Ca^{2+} concentration increases cardiac contractility. 3) In toxic doses, intracellular calcium elevates further and triggers afterdepolarizations. This increases the risk of arrhythmias while shortening the refractory period and increasing automaticity 4) Digoxin also has neurohormonal effects, which increases parasympathetic tone. Increased vagal tone leads to stronger atrioventricular nodal blockade, leading to more uncontrolled arrhythmia. and increasing the myocardial refractory period through vagal tone stimulation[35]. Therefore, digitalis toxicity can cause variable types of arrhythmias such as; supraventricular and ventricular tachycardia, atrial fibrillation and flutter, ventricular fibrillation, extrasystole and heart block [36]. There are multiple factors that could increase incidence of digitalis toxicity including; renal insufficiency, patients with advanced age, MI and thyroid disorders, electrolyte imbalance and there are also medications which enhance digitalis toxicity like; diuretics, amiodarone, beta-blockers, benzodiazepines, calcium channel blockers, macrolide antibiotics, propylthiouracil and amphotericin [37].

Conclusion:

Toxic agents have a very harmful effect on the heart producing cardiomyopathy and heart failure. A lot of drugs and environmental toxins can produce cardiotoxicity including; anti-cancer drugs, anti-diabetic drugs, cocaine, ethanol, CO, and heavy metals. Mechanisms by which these agents produce cardiomyopathy are very complicated and include many factors such as mitochondrial toxicity. Eventually all the mechanism lead to increase work rate of the heart as compensation for degeneration leading to heart failure. The main way to prevent this condition is isolation of patient from toxic agents and treat the cardiovascular diseases produced.

Conflicts of interests: The Authors declare that there are no conflicts of interests.

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