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Review Article

ROLE OF CERTAIN DRUGS IN CARDIOTOXICITY INDUCTION FOR THE EXPERIMENTAL PURPOSE

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ABSTRACT

Cardiovascular diseases are caused by disorders of the heart and blood vessels and it remains the principal cause of death in both developed and developing countries, accounting for roughly 20%. Cardiotoxicity renders the heart unable to efficiently pump blood throughout the body. Oxidative stress resulting from the higher production of free radicals that plays a major role in cardiovascular disease. Cardiotoxicity is described as the harmful effect on the heart caused by various drugs. Anticancer drugs, antipsychotic drugs, methamphetamine, isoproterenol, minoxidil, cyclosporine A, azithromycin, tilmicosin etc., can able to produce cardiotoxicity by various mechanisms. In this context, we have made an attempt to explore the therapeutic drugs induced cardiotoxicity in experimental animal models with their dose and mechanism.

Keywords: Cardiotoxicity, Oxidative Stress, Screening Technique

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INTRODUCTION

Cardiovascular diseases remain the principal cause of death in both developed and developing countries, accounting for roughly 20% of all worldwide deaths per year [1]. According to world health organization, it is predicted that Cardiovascular diseases will be the most important cause of mortality in India by 2020 [2]. Cardiovascular diseases caused by disorders of the heart and blood vessels, and include coronary heart disease, stroke (cerebrovascular disease), hypertension, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure [3]. Among several cardiovascular diseases particularly myocardial infarction has become a major public health problem in western and industrialized countries and also increasingly in developing countries such as India and makes a significant contribution to the mortality statistics [4].

Myocardial infarction is an acute condition of necrosis of the myocardium that occurs as a result of an imbalance between myocardial demand and coronary blood supply [5]. It is well established that reactive oxygen species (ROS) have been implicated in the pathophysiology of myocardial infarction [6]. Myocardial infarction symptoms such as acute coronary syndrome, chest pain, sweating, palpitations and anxiety. Complications of myocardial infarction include arrhythmias, congestive heart failure, cardiogenic shock, ventricular aneurysm and pericarditis [7].

Cardiotoxicity is the occurrence of heart electrophysiology dysfunction and/or muscle damage. The heart becomes weaker and is not as efficient in pumping and therefore circulating blood. Cardiotoxicity is described as the harmful effect on the heart caused by various drugs. The National Cancer Institute defines cardiotoxicity in very general terms as "toxicity that affects the heart". It provides a direct effect of the drug on the heart and also an indirect effect due to the enhancement of hemodynamic flow alterations [8].

Oxidative stress resulting from the higher production of free radicals that plays a major role in cardiovascular diseases such as myocardial infarction, ischemic heart disease, atherosclerosis, congestive heart failure, cardiomyopathy and arrhythmias. Studies have been shown that there is an increased generation of ROS such as superoxide anion and hydroxyl radicals in heart failure which are involved in the formation of lipid peroxides, damage of cell membrane and destruction of antioxidative defence system [9].

Search criteria

In this review, articles were included from Google Scholar, Research gate, Science Direct and PubMed databases and by using several keywords for search: cardiotoxicity, cardiovascular diseases, Oxidative Stress. Articles between the years of 1986 to 2017 were selected for reviewing.

Experimental models

The commonly used animals for *in vivo* studies include mouse, rat, rabbit, pig, and dog. These animal studies enable repeated administration of chemotherapeutic drugs produces chronic cardiotoxicity. Transgenic animal models also used to study the cardiotoxicity. For example, Hfe-deficient mice showed increased susceptibility to doxorubicin-induced cardiotoxicity, proposed the significance of iron in cardiotoxicity [10]. Another approach is the use of *in vitro* cell culture models including isolated cardiac myocytes, cardiomyocyte-derived cell lines, particularly primary neonatal rat cardiomyocytes and less often adult cardiomyocytes [11]. Experimental induction of cardiotoxicity by drugs in animals is a well-established model to study the protective role of different cardioprotective agents.

Chemotherapy-induced cardio toxicity

Chemotherapy is a common treatment for various cancers as a primary therapy. The basic principle of chemotherapy is to impair the mitotic and metabolic process of cancer cells. Though few newer chemotherapeutic agents are highly effective in treating most cancers, such agents are associated with cardiotoxicity ranging from mild transient blood pressure change to potentially serious heart failure [12]. There is a high prevalence of cardiotoxicity from cytotoxic treatment [13].

Anthracyclines

Anthracycline antibiotics, such as doxorubicin and epirubicin are potent, broad-spectrum chemotherapeutic agents that are highly effective against haematological malignancies and a variety of solid tumors [14].

Doxorubicin is an anthracycline antibiotic produced by *Streptomyces peucetius.* Administration of doxorubicin caused various toxicity such as hematopoietic suppression, nausea, vomiting, extravasation, alopecia and cardiotoxicity [15].

Epirubicin is an anthracycline antibiotic that differs from doxorubicin in the epimerisation of the OH group in position 4' of the amino-sugar moiety. Epirubicin was less cardiotoxic than doxorubicin [16]. Anthracyclines operates on many levels by different mechanisms:

Oxidative stress hypothesis

The major mechanism of chemotherapy-induced cardiotoxicity is a generation of ROS. Increased ROS that causes cellular damages and alteration responses, referred to as oxidative stress which occurs when the difficult balance of the ROS-generating system and antioxidant defence system [17]. Due to low levels of antioxidant enzymes in the heart, there would be a susceptibility of the cardiac cells to the oxidative stress. [18].

Metabolite theory

Cancer patients often have a spontaneous exacerbation of lipid peroxidation and doxorubicin inhibits this effect in a convoluted way [19].

Influence on calcium homeostasis

Another possible mechanism involves the influence of anthracyclines on the calcium homeostasis. Anthracyclines could stimulate the release of calcium from isolated cardiac and skeletal muscle sarcoplasmic reticulum vesicles. *In vitro* experiments showed that doxorubicin treatment caused an irreversible decrease in mitochondrial calcium loading capacity [20].

Role of immune system

Doxorubicin caused a damaged plasma membrane of cardiac myocytes with an enhanced immune response [21].

Role of mitochondria

Mitochondria were mediated by the enzymatic pathway for the formation of free radicals. Doxorubicin has a high affinity for cardiolipin, a phospholipid in the internal membrane of mitochondria. This thing permitted doxorubicin to induce the cardiotoxicity. Animal studies showed that apoptotic cell death occurred *in vivo* after administration of doxorubicin [22].

Cyclophosphamide

Cyclophosphamide, a cytotoxic alkylating agent, is used as an antineoplastic agent for the treatment of haematological malignancies and a variety of solid tumours including leukaemia, ovarian cancer, small cell lung cancer and immunosuppressive agent [23]. High dose of cyclophosphamide is used in transplant regimens and combined with acute cardiotoxicities such as cardiac decompensation and fatal cardiomyopathy [24]. The pathogenesis of cyclophosphamide is an increase in free oxygen radicals that to play a role in oxazaphosphorine induced cardiotoxicity. This increase would be mediated by elevated intracellular levels of the actual cytotoxic metabolite phosphoramide mustard [25].

Cisplatin

Cisplatin is an antitumour agent against several types of cancer. The effect of cisplatin has been determined against a variety of tumours such as head and neck, testicular, ovarian, bladder and small cell lung cancers. Even though it produces beneficial effects it also causes some adverse effects such as nephrotoxicity, hepatotoxicity and spermiotoxicity [26]. Several factors have been reported are vascular damage, alterations in platelet aggregation and hypomagnesemia [27-30]. In experiments on animal platelets, cisplatin was able to trigger platelet aggregation and/or enhance thromboxane formation by platelets. Activation of an arachidonic pathway in platelets by cisplatin seemed to be involved [31].

5-Fluorouracil

5-Fluorouracil is an antimetabolite that acts during the S phase of the cell cycle. 5-Fluorouracil is activated by thymidine phosphorylase into fluorodeoxyuridylate that inhibits thymidylate synthase, thus preventing DNA synthesis; that leads to imbalanced cell growth and ultimately cell death [32]. 5-Fluorouracil is still a widely used in the treatment of colon cancer, breast and other cancers like head and neck [33]. The mechanism of 5-FU associated cardiotoxicity is ischemia to the myocardium, cardiotoxic impurities in the 5-FU formulation (fluoroacetaldehyde, generated in the alkaline solution of fluorouracil during storage, which may be converted to a cardiotoxic agent, fluoroacetate), protein kinase C (PKC)-mediated vasoconstriction and free radical damage to the myocardium [34-37].

Antipsychotic drugs induced cardiotoxicity

Several antipsychotics including typical and atypical could be effective for the treatment of mental illness but caused cardiovascular side effects such as arrhythmias, hypertension, myocarditis, and orthostatic hypotension. Myocarditis is rare but potentially fatal complications of antipsychotic therapy. This disorder has been demonstrated with clozapine [38]. Clozapine, a tricyclic dibenzodiazepine, belongs to the class of second-generation antipsychotics. The exact mechanisms of clozapine-induced cardiac toxicity are not yet fully known. The pathogenesis of this toxic reaction is attributed to increased myocardial oxidative stress, inflammatory cytokines and oxidative DNA damage [39]. Some other drugs such as amisulpride, haloperidol, levomepromazine, olanzapine, risperidone induce cardiac lesions in rabbit [40].

Methamphetamine-induced cardiotoxicity

Methamphetamine possesses a high potential for abuse and addiction and has become a serious social problem worldwide [41]. Methamphetamine is a stimulant which acts by stimulating the release of catecholaminergic neurotransmitters in both the central and peripheral nervous systems. The pathophysiologic mechanism of meth-amphetamine-induced cardiotoxicity is the induction of sympatho-mimetic effects on central and peripheral nervous system which leads to elevation of circulating catecholamine concentration [42]. High concentration of catecholamine causes narrowing and spasm of the blood vessels, tachycardia, hypertension and probably the death of the cardiomyocyte [43].

Isoproterenol-induced cardiotoxicity

Isoproterenol [1–(3, 4–dihydroxyphenyl)–2–isopropylaminoethanol hydrochloride] is a synthetic catecholamine and -adrenergic agonist that is an important regulator of myocardial contractility and this is the standard model to study the beneficial effects of several drugs on cardiac function [44]. The pathophysiologic mechanism of isoproterenol induces cardiac necrosis by several mechanisms which are oxidative stress, alterations in metabolism, coronary insufficiency, functional hypoxia and ischemia, increased calcium overload, changes in electrolyte contents and decreased lethe vel of high energy phosphate stores, catecholamine autoxidation and lipid peroxidation [45-47].

Minoxidil induced cardiotoxicity

Minoxidil is a potent long-acting vasodilating drug which lowers arterial blood pressure by a direct action on arteriolar smooth muscle. Minoxidil has been associated with signs of reflex sympathetic activation such as tachycardia, increased venous return and increased cardiac output. Minoxidil causes 3 morphologically distinct cardiovascular lesions in the dog [48].

1. Coronary arterial medial haemorrhage and necrosis,
2. Subendocardial necrosis, and
3. Right atrial hemorrhagic lesions

Cyclosporine an induced cardiotoxicity

Because of its specific inhibiting effect on the signal transduction pathways of the T cell receptor, cyclosporine A is the mostly used immunosuppressor agent and also used in the treatment of autoimmune diseases. Even though the drug produces beneficial effects; they are associated with some adverse effects like nephrotoxicity, hypertension, hepatotoxicity and cardiotoxicity. The pathophysiologic mechanisms by which cyclosporine A-induced cardiotoxicity are still unknown, but recent studies have been reported that oxidative stress may play a major role [49].

Azithromycin-induced cardiotoxicity

Azithromycin is a broad spectrum second generation macrolide antibiotic, which is frequently used in the treatment of bacterial infections. The pathophysiologic mechanisms are oxidative stress, cytokine release and apoptotic cell death [50, 51].

Tilmicosin induced cardiotoxicity

Tilmicosin is a semi-synthetic macrolide antibiotic widely used in veterinary medicine. Even though macrolide antibiotics are considered safe, cardiotoxic effects of tilmicosin were identified in various animal species. Pathophysiologic mechanism of cardiotoxicity is increased oxidative stress, increased calcium overload and myocardial apoptosis [52-54].

Table 1: Dose and treatment of drugs inducing cardiotoxicity

Drugs	Dose	Treatment
Doxorubicin	15 mg/kg	Treatment of test drug for 10 d. A single dose of doxorubicin on 7th d [55]
	7.5 mg/kg	Treatment of test drug for 10 d. A single dose of doxorubicin on 5th d [56]
	20 mg/kg	Test drug for 14 d. Single dose after 14th d [57]
	2.5 mg/kg	Extract of test drug treatment for 25 d. Doxorubicin treatment on 1, 7, 14, 21, 28th d [58]
	1.5 mg/kg	Doxorubicin treatment of 8 w for a total cumulative dose of 12 mg/kg body weight[59]
	3 mg/kg	Test drug treatment for 11 d. Doxorubicin injected only on d 1, 7 and 11[60]
	4 mg/kg	Doxorubicin-treated weekly once for 4 w. The test drug-treated orally, twice a day for 7 w[61]
	10 mg/kg	Test drug administered for 10 continuous d. Doxorubicin was injected on 7th day [62]
	20 mg/kg	Drug treatment for 14 d and doxorubicin-treated after the last dose of test drug [63]
	5 mg/kg	Doxorubicin 5 mg/kg, weekly for 3 w [64]
Epirubicin	10 mg/kg	A single dose of epirubicin on day 1 and test drug for 10 d [16]
Cyclophosphamide	200 mg/kg and 150 mg/kg	A single dose of cyclophosphamide injected on the first day of the experimental period and test drug was treated for 10 d [23]
Cisplatin	7 mg/kg	Experimental design for 10 d and a single dose of cisplatin injected [26]
5-Fluorouracil	150 mg\kg	Experimental design for 8 d and a single dose of 5-fluorouracil administered on 5th day [65]
	20 mg/kg	Test drug and 5-fluorouracil administered for 30 d [66]
Clozapine	10, 15 and 25 mg/kg	Animal were treated with clozapine for 21 d [39,67]
Amilspuride	15 mg/kg	Toxicants treated for 3 mo [40]
Haloperidol	0.20 mg/kg	Experimental design for 3 mo and toxicant for injected daily [40]
Risperidone	1 mg/kg	Experimental design for 3 mo and risperidone was treated every 15 d [40]
Olanzapine	0.3 mg/kg	Olanzapine-treated daily for 3 mo [40]
Levomepromzine	3 mg/kg	Experimental design for 3 mo and levomepromazine was administered daily for 3 mo [40]
Methamphetamine	30 mg/kg	Methamphetamine injected for animals and sacrifice after 6 h [41]
	3 mg/kg/d	Test drug and methamphetamine were treated for 8 w [68]
	5 mg/kg	Methamphetamine was administered and test drug was administered 30 min before Methamphetamine and sacrifice after 24 h [69]
Isoproterenol	100 mg/kg	Test drug treat orally daily for 14 d and isoproterenol was subcutaneously injected at an interval of 24 h on 15th and 16th day [70]
	200 mg/kg	Drug treatment for 7 d and isoproterenol-treated for last 2 d [71]
	85 mg/kg	Rats were treated with test drug for a period of 15 d and isoproterenol was administered consecutively on d 13 and 14 [72] Rats were treated with test drug for 30 d and isoproterenol was administered at a dosage of 85 mg/kg per 24 h for 2 d [80]
	60 mg/kg	Drug treatment for 30 d and isoproterenol-treated at an interval of 24 h for two d [73]
	150 mg/kg	Test Drug for 30 d and injection of isoproterenol at last 2 d [74]
	20 mg/kg	Test drug treatment for 30 d. At the end of the treatment period, all groups were administered with isoproterenol twice at an interval of 24 h [75]
	5 mg/kg	Drug treatment orally for 14 d and isoproterenol 5 mg/kg/day for 14 d subcutaneously [76]
	0.5,1, 3 mg/kg	Single oral dose of 2 consecutive d [48]
Minoxidil	10,50,250 mg/kg	Minoxidil administered on two consecutive d [77]
Cyclosporine A	25 mg/kg	Test drug and cyclosporine A were administered daily for 21 d [49]
Azithromycin	15 mg/kg and 30 mg/kg	Azithromycin was orally administered to rats for 14 d [78]
	10 mg/kg	Test drug for 5 d before azithromycin administration and 5 d thereafter [50]
Tilmicosin	75 mg/kg	Test drug administered for 5 d and a single dose on 5th d [79]

Kg: kilogram; mg: milligram; h-hour

CONCLUSION

Various studies showed that drugs such as anticancer drugs (doxorubicin, cyclophosphamide, cisplatin, epirubicin, 5-Fluorouracil), Antipsychotic drugs, methamphetamine, iso-proterenol, minoxidil, cyclosporine-A, azithromycin, tilmicosin produce cardiotoxicity in various animal models. The patho-physiologic mechanism of these drugs induces cardiac necrosis by several mechanisms which are oxidative stress, increased calcium overload, inflammatory cytokines, apoptotic cell-death, coronary insufficiency, functional hypoxia and ischemia.

Among these mechanisms, oxidative stress plays a major role in drugs induced cardiotoxicity. These drugs are used to induce cardiotoxicity in various animals for cardio protective studies.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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