Research Article

Biochemical and pharmacological estimation of erythrosine in myocardial remodeling among heart failure induced by doxorubicin in rats

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Abstract

Objective: Myocardial remodeling is the distinction of genome expression, molecular& cellular interstitial changes, and major myocardial (myocyte) that are actually responsible for changes in size, shape, heartbeat and other relevant processes includes ischemia, cell necrosis, and apoptosis. The present study was designed as the biochemical and pharmacological estimation of erythrosine in myocardial remodeling among heart failure induced by doxorubicin in the rat. **Materials and Methods:** Albino Wistar rats (100-150gm) were divided into 4 groups (n=6), normal control group rats were only administered with normal diet/normal saline and themyocardial remodeling were induced by a single dose of Doxorubicin (1.25mg/kg) with the association of fasting condition. The oral dose of erythrosine 0.25mg/kg and treatment drug i.e. Doxorubicin+Erythrosine were administered for the period of 16 weeks. **Results:** The description of the present study suggests that the CPR level (2.10±0.05 mg/dl) of erythrosine may probably control the myocardial remodeling, Creatinine level of erythrosine (0.722±0.009 mg/dl) control rat may responsible to maintain the normal myocardial function. The improvement in cholesterol (71.67±1.382 mg/dl) and triglyceride (59.50±1.746 mg/dl) levels in the treatment group may responsible for normal myocardial function. Troponin-T value (0.615±0.028 ng/ml) and CPK-MB value (593.7±5.81) of the treatment group is reported as sensitive in acute heart failure. **Conclusion:** Administration of Doxorubicin at single dose altered all biochemical parameters that are responsible for myocardial remodeling. From the findings of results, it is very clear that oral administration of Erythrosine may promote myocardial remodeling in the animal model.

Keywords: Myocardial remodeling, heart failure, doxorubicin, erythrosine, troponin-T

Introduction

Myocardial remodeling is usually accepted as a determinant of the clinical course of heart failure (HF). The distinct genome expression influences molecular, cellular, and interstitial changes and clinically manifested as changes in size, shape, and performance of heart that observed from a myocardial output. The myocardial remodeling inclined by the close investigation of hemodynamic load, neurohormonal activation, and alternative factors responsible for myocardial injuries (Cohn et al., 2000).

Ischemic injury provoked by acute myocardial infarction (MI) is typically followed by a wound repair method of the left ventricle referred to post-infarction left ventricle remodeling (LVR). Extent myocardial remodeling seen in both infarcted and non-infarcted myocardium recognized as the major determinant of the development of HF and might be a predictive factor for mortality and morbidity in patients with MI. The remodeling process contributes to hypertrophy, inflammatory response, and connective tissue changes (Vilahur et al., 2011).

The myocyte is the major myocardial cell involved the remodeling process and other components included the interstitial, fibroblasts, collagen, coronary vasculature, and relevant processes include ischemia, cell necrosis, and apoptosis (Paula et al., 2016).The burden of heart failure (HF) represents the inability of the heart to respond to the circulatory demand of the organism. The main causes of HF

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are hypertension, ischaemic and valvular injuries whereas toxic, metabolic or genetic origins are less common (Savarese and Lars, 2017). Addition to the initial abnormality, secondary changes occur over the course leading to the multi-organ impairment (Heinzel et al., 2015).

The factors that influencing remodeling other than the related exclusively is the renin-angiotensin system (RAS) and sympathetic nervous system (SNS) currently under investigation & include endothelin, cytokines and the nitric oxide production and oxidative stress (Duprez, 2006).

The prevalence of the HF estimated as more than 20 million people suffer worldwide globally and constantly increasing because of an aging population, the success rate in prolonging survival of patients suffering from the coronary event are at high risk (Gruson et al., 2011). It has been estimated that 0.4–2.2% of the population in industrialized countries suffer from HF, with between 500,000–600,000 incident cases diagnosed each year. HF affects especially the elderly, with 80% of HF-related hospitalizations and 90% of HF-related deaths occurring among patients aged 65 years or older. The prevalence of HF has increased over the past decades (Lesyuk et al., 2018).

The global economic burden of HF is estimated at $108 billion per annum, with $65 billons attributed to direct and $43 billons to indirect costs. The US is the biggest contributor to the global HF costs and is responsible for 28.4% of total global HF spend. Europa accounts for 6.83% of total global HF costs (Cook et al., 2014). Approximately one in four HF patients among the Medicaid beneficiaries in the U.S. are immediately readmitted after discharge from the hospital because of the onset of HF are strongly correlated with aging, and the prevalence is expected to grow worldwide with this population (Lee et al., 2016).

Erythrosine commonly referred to as red dye is an artificial red food coloring made from coal tar containing organic compound i.e. iodine and sodium. It is also called xanthene dyes because the base contains xanthene molecule provided that a group of brilliant fluorescent dyes ranging color from yellow to pink to bluish red (Ryvolova et al., 2007). Doxorubicin is also known as hydroxyl-daunorubicin and hydroxy-daunomycin, a drug used in cancer chemotherapy and derived by chemical semi-synthesis from bacterial species. It is anthracycline antitumor antibiotic closely related to natural product daunomycin and like all anthracyclines, works intercalating DNA, the most serious adverse effect being life-threatening heart damage. It is commonly used in the treatment of a wide range of cancers, including hematological malignancies, many types' carcinoma, & soft tissue sarcomas. It is often used in combination chemotherapy as a component of various chemotherapy regimens (Cram, 2017).

Materials and methods

Experimental animals

Albino Wistar rats of either sex weighing between 100-150gm were procured from IVRI, Izzatnagar, Bareilly. The animals were housed under standard conditions of temperature ($25\pm2^{\circ}$C) and relative humidity (30-70%) with a 12h light-dark cycle and acclimatized in the institutional animal house. The animals were fed with standard diet and purified water. The animals approved by the IAEC Committee of Siddhartha Institute of Pharmacy, Dehradun were taken for conducting the activity.

Procurement of drug and chemicals

All the drug and chemical were procured from local as well as national supplier such as; Doxorubicin and Erythrosine was purchase from IPCA Laboratories Ltd. Mumbai, while other chemical used in the study purchase from local supplier Dehradun.

Experimental design

All the animals were divided into 4 groups with 6 animals in each group. Group I served as Normal control (NC) only administered with normal diet/normalsaline; Group II as Doxorubicin control (DC) administered a single dose of Doxorubicin (1.25mg/kg); Group III as Erythrosine control (EC) administered erythrosine (0.25mg/kg); and Group IV as a treatment drug i.e. Doxorubicin+Erythrosine (D+E) rats were administered with a single dose of Doxorubicin (1.25mg/kg) followed by Erythrosine (0.25mg/kg)received treatment for 16 weeks.

Induction of myocardial remodeling

Myocardial remodeling was induced by administration of a Doxorubicin (single dose of 1.25 mg/kg b.w.) with the association of fasting condition.

Estimation of biochemical parameter

Blood sample was collected at the end of the experiment from retro-orbital plexus under light ether anesthesia without any anticoagulant and allowed to stand for 30 minutes at room temperature then centrifuged at 250rpm for 10 minutes to separate the serum. The obtained serum was kept at 4°C until used for analysis. The estimation of serum total cholesterol, triglyceride, HDL, and LDL was performed using the standard kit (Siemens healthcare diagnostics ltd.) with a semi-auto analyzer (photometer 5010, Nicholas India Pvt. Ltd).

Statistical analysis

Statistical analysis was carried out using Graph Pad Prism 5.0 (Graph Pad Software, San Diego, CA, USA). The results were expressed as mean±SEM. Statistical

significance between more than two groups was tested using one-way ANOVA followed by Turkey's multiple comparison tests. Values of p<0.05 were considered significant.

Results and discussion

Estimation of CRP and Creatinine

C-reactive protein (*CRP*) is a substance produced by the liver in response to inflammation as biomarkers in the body. The *Creatinine* probably modified treatment in *response* to myocardial remodeling. The elevated levels of serum parameters showing the comparison of CRP and Creatinine level in normal control (NC) and Doxorubicin control (DC) with treatment group are given in table 1.

Table 1. Effect of Doxorubicin and Erythrosine on CRP and Creatinine level in rats

Groups	CRP (mg/dl)	Creatinine (mg/dl)
Normal control (NC)	1.53 ± 0.10	0.817 ± 0.008
Doxorubicin control (DC)	$2.80 \pm 0.09^{\#}$	0.835 ± 0.011^{ns}
Erythrosine control (EC)	$2.10 \pm 0.05^{**}$	$0.722 \pm 0.009^{**}$
Doxorubicin+Erythrosine control (DC+EC)	2.90 ± 0.05^{ns}	0.872 ± 0.015^{ns}

Values are expressed as mean$\pm$SEM (n=6). $^{\#}$p<0.05as compared to normal control, **p<0.05 as compared to Doxorubicin control, and ns: non significant

The observed results were stated that the CRP level showed a significant increase ($^{\#}p<0.05$) in Doxorubicin control (DC) group as compared to NC group, while the Erythrosine treated group shows significant improvement($^{**}p<0.05$)in CRP level (2.10±0.05 mg/dl) as compared to DC group. The treatment group (DC+EC)shows no-significant *(ns)*change in CRP level when compared to the DC group. The study reveals that the Creatinine showed non-significant *(ns)* change in Doxorubicin control (DC) group as compared to NC group, while the Erythrosine treated group shows significant improvement ($^{**}p<0.05$) in Creatinine concentration (0.722±0.009 mg/dl) as compared to DC group. The treatment group (DC+EC) also shows non-significant *(ns)* change in CRP level when compared to the DC group (table 1).

Estimation of HDL and LDL

The high LDL with low HDL level is an additional risk factor for cardiovascular disease. The results of the present study show thenormal value of HDL is 14.33±0.803 mg/dl and LDL value i.e.51.50±0.764 mg/dl given in table 2.

In Doxorubicin Control (DC) group the HDL and LDL level was showed non-significant*(ns)* change as compared to NC group, and the Erythrosine control (EC) group also showed non-significant *(ns)* change in these parameters as compared to DC group. While the treatment groups showed statistically significant change ($^{**}p<0.05$) in HDL level (10.67±0.494 mg/dl)

in comparison to DC group, but LDL level (49.67±1.54 mg/dl) did not show significant *(ns)*change when compared to DC group (table 2).

Table 2. Effect of Doxorubicin and Erythrosine on HDL and LDL level in rats

Groups	HDL (mg/dl)	LDL (mg/dl)
Normal control (NC)	14.33 ± 0.803	51.50 ± 0.764
Doxorubicin control (DC)	13.00 ± 0.577	39.67 ± 1.82^{ns}
Erythrosine control (EC)	13.50 ± 0.764^{ns}	35.33 ± 1.05^{ns}
Doxorubicin+Erythrosine control (DC+EC)	$10.67 \pm 0.494^{**}$	49.67 ± 1.54^{ns}

Values are expressed as mean$\pm$SEM (n=6). $^{\#}$p<0.05 as compared to normal control, **p<0.05 as compared to Doxorubicin control, and ns: non-significant

Estimation of Cholesterol and Triglyceride

Cholesterol is a lipid molecule and biosynthesized by all animal cells because it is an essential component of animal cell membranes that required maintaining both membrane structural integrity and fluidity. Triglycerides are one type of lipids transported in the bloodstream and generally body fats stored in triglycerides form in the tissues. Always the serum levels of triglyceride are regularly measured along with cholesterol. The results of the present study show the normal value of cholesterol is 76.00±0.8944 mg/dl and triglyceride value i.e. 85.17±1.078 mg/dl given in table 3.

Table 3. Effect of Doxorubicin and Erythrosine on cholesterol and triglyceride level in rats

Groups	Cholesterol (mg/dl)	Triglyceride (mg/dl)
Normal control (NC)	76.00 ± 0.8944	85.17 ± 1.078
Doxorubicin control (DC)	$61.00 \pm 1.880^{\#}$	$56.00 \pm 1.932^{\#}$
Erythrosine control (EC)	56.33 ± 0.8819^{ns}	54.00 ± 0.9661^{ns}
Doxorubicin+Erythrosine control (DC+EC)	$71.67 \pm 1.382^{**}$	59.50 ± 1.746^{ns}

Values are expressed as mean$\pm$SEM (n=6). $^{\#}$p<0.05 as compared to normal control, **p<0.05 as compared to Doxorubicin control, and ns: non significant

In Doxorubicin Control (DC) group the cholesterol and triglyceride levels were significantly ($^{\#}$p<0.05) decreases as compared to NC group, while the Erythrosine control (EC) group showed non-significant*(ns)* change when compared to DC group. The treatment group (DC+EC) showed significant ($^{**}p<0.05$) improvement in cholesterol level (71.67±1.382 mg/dl) as compared to NC group, while the triglyceride level (59.50±1.746 mg/dl) didn't show significant *(ns)* improvement in comparison to NC group (table 3).

Estimation of Troponin-T and CPK/MB

Troponins are an essential protein molecule of myocardial

and skeletal muscle but not of smooth muscle cells. Troponins generally undetectable in healthy patients, although it may eventually change as more sensitive assays become available. The CPK-MB also a marker of myocardial remodeling used to assist in the diagnosis of acute myocardial infarction. The CK-MB levels in serum measured as the bound combination of two variants (isoenzymes CKM and CKB) of the enzyme phosphocreatine-kinase (table 4).

Table 4. Effect of Doxorubicin and Erythrosine on Troponin T and CPK/MB level in rats

Groups	Troponin-T (ng/ml)	CPK/MB
Normal control (NC)	0.718 ± 0.009	292.2 ± 2.11
Doxorubicin control (DC)	0.730 ± 0.027^{ns}	$180.2 \pm 22.58^{\#}$
Erythrosine control (EC)	$3.88 \pm 0.060^{**}$	$593.7 \pm 5.81^{**}$
Doxorubicin+Erythrosine control (DC+EC)	0.615 ± 0.028^{ns}	176.7 ± 6.67^{ns}

Values are expressed as mean$\pm$SEM (n=6). $^{\#}$p<0.05 as compared to normal control, **p<0.05 as compared to Doxorubicin control, and ns: non-significant

In Doxorubicin control (DC) group the TROP-T level (0.730 ± 0.027ng/ml) and CPK/MB level (180.2 ± 22.58) were showed non-significant *(ns)* change as compared to NC group; While Erythrosine treated group, both the TROP-T level (3.88 ± 0.060ng/ml) and CPK/MB level (593.7 ± 5.812) were observed as significantly($^{**}p<0.05$) increased as compared to DC group. The treatment (DC+EC) group didn't show non-significant *(ns)* improvement in both parameters as compared to other groups (table 4).

Myocardial remodeling is associated with myocardial rupture, ventricular aneurysm, an increased risk for progressive ventricular dysfunction, and cardiovascular death after MI (Galli and Lombardi, 2016). In the acute phase, ventricular dilation is a result of the infarction expansion process, whereas late cavity dilation is the result of the eccentric hypertrophy process (Kerkhof, 2015). Therefore, several variables have been used to predict the remodeling process in the acute phase of MI, such as infarct size, infarct location, previous infarct, wall stress, neurohumoral activation, diabetes mellitus, hypertension, decreased ejection fraction, and signs of heart failure (Zornoff et al., 2009).

C-reactive protein (CRP) is an annular, pentameric protein found in blood plasma, and the increased level highly responsible for inflammation (Bansal et al., 2014). It is recognized as an acute-phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells (Serrano et al., 2018). The physiological role is to bind with lysophosphatidylcholine expressed in the surface of dying cells in order to activate the complement system by the C1Q complex. The high level ($\geq$ 3.0 mg/dl) of CRP causing the risk of

developing cardiovascular disease (Gang et al., 2012), our finding suggests that the CPR level (2.10 ± 0.05 mg/dl) of erythrosine treated rat may probably control the myocardial remodeling.

The normal level of Creatinine in the blood is approximately 0.6–1.2 mg/dl in adult males and 0.5–1.1 mg/dl in adult females (Vadde, 2013). The description of the present study suggests that the Creatinine level of erythrosine (0.722 ± 0.009 mg/dl) group may somewhat responsible to maintain the normal myocardial function and also play a crucial role in myocardial remodeling.

The HDL typically composed of 80-100 proteins per particle and transporting to hundreds of fat molecules per particle. Unlike the larger lipoprotein which delivers fat molecules to cells, HDL particles remove fat molecules from cells which need to export fat molecules (Bibow et al., 2017). The fats carried include cholesterol, phospholipids, and triglycerides; amounts of each are quite variable (Barter et al., 2007).

The observed result from present study confirms that the HDL value in erythrosine control (13.50 ± 0.764 mg/dl) group and LDL value in erythrosine control (35.33 ± 1.05 mg/dl) group have not maintained the normal range and fall to achieve the significant improvements in doxorubicin-induced myocardial remodeling. High LDL with low HDL level is an additional risk factor for cardiovascular disease. Cholesterol enables animal cells to dispense with cell wall thus allowing animal cells to change shape and regulate the movement of muscle (Vergeer et al., 2010). The study reveals the cholesterol level (71.67 ± 1.382 mg/dl) and triglyceride level (59.50 ± 1.746 mg/dl) in the treatment group and the changes in these levels may responsible for the improvement in myocardial function.

The 99% cut off point for myocardial Troponin-T is well-known at 0.01 ng/ml with 10% coefficient of variance value at the 99%is0.03 ng/ml (Xu et al., 2013). The finding of the present study reported as the value of Troponin-T in the treatment group is 0.615 ± 0.028 ng/ml. There is an increasing scientific interest in the development of novel, sensitive and high-sensitivity (hs) assays of Troponin T (hs-TnT). The emerging hs-TnT seems quite promising in detecting even slight amounts of myocardial injury. Previous investigators supported the short- and long-term predictive power of sensitive Troponin in acute heart failure. It is well-known that elevated conventional TnT levels implicate poor prognosis and increased the severity of symptoms and left ventricular dysfunction in patients with stable chronic HF.

The result of the present study reveals that the CPK-MB

value is 180.2±22.58 in doxorubicin and 593.7±5.81 in Erythrosine group. Increasing the enzyme is also described in young persons with left ventricular hypertrophy and myocardial chambers enlargement during physical training. The data presented here supported the hypothesis; synthesis of CK-MB also increases in the failing myocardium and left ventricular failure.

Conclusion

The researchers are very apparent from their study that the erythrosine and doxorubicin may possibly induce ventricular dysfunction that leads to myocardial infarction and for a short period it favours to convert in myocardial remodeling. In which the size of the tissue is significantly enlarged and responsible for the augmented amount of phospholipids production that's directly related to increasing the level of LDL and decreased the level of HDL in serum, which is responsible for removing unwanted cholesterol from the blood into the urine. If the level decreases it would be directly responsible for the rise of unwanted cholesterol level in the body. This unwanted cholesterol would be lead in the formation of Phospholipids, ultimately accountable in the formation of Plasma membrane. Current research work is giving a glimpse that erythrosine clearly promotes the myocardial remodeling by altering various biochemical markers such as Troponin-T, CRP, and Triglyceride. These myocardial markers indicate the injury, infection, and inflammation in the body, whether the increased level of CRP is directly related to inflammation (Shrivastava et al., 2015). Hence, erythrosine is efficient in reducing these elevated levels of CRP to the normal indicating its competence towards the normal function of the heart. Erythrosine may stimulate the vascular inflammation by various circulating pro-inflammatory cytokines such as interleukin-6, interleukin 1-beta (Sprague and Khalil, 2009). These cytokines may increase the nitric oxide synthase (NOS) expression and nitrite production that generates ROS formation and subsequent MAPK development, which may lead oxidation of myofilaments and induced apoptosis in cardiomyocyte. Furthermore, the rigorous research is essential for the appreciation of the fruitful role of erythrosine as a promoter of myocardial remodeling.

Acknowledgment

Conflicts of interest

The authors declare no conflicts of interest.

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