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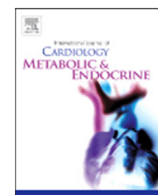

Prevention of Adriamycin induced cardiotoxicity in rats — A comparative study with subacute angiotensin-converting enzyme inhibitor and nonselective beta blocker therapy

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ABSTRACT

Back ground: Cardiotoxicity confines the usage of Adriamycin in clinical practice as it can develop cardiac impediments up to 10 years after the termination of therapy. Even though, no specific therapeutic strategies are available for treating adriamycin-induced cardiotoxicity, beta-adrenergic blockers (βB) and angiotensin-converting enzyme (ACE) inhibitors are known to prevent its progression into failure. In this scenario, we attempted to compare the pharmacological outcome of sub-acute βB and ACE inhibitor treatments in preventing adriamycin-induced cardiotoxicity by analysing the differences between them.

Methods: Rats received a single bolus dose of adriamycin (10 mg/kg) on day one and treated with either Carvedilol (10 mg/kg) (CAR) or Captopril (50 mg/kg) (CAP) once daily for 28 days. Cardiac morphology, systolic and diastolic functions were evaluated by 2D trans-thoracic echocardiography. Cardiac Troponin and Ck MB levels were measured to analyse the myocyte damage. Myocardial lipid peroxidation, IL1β levels and caspase 3 activity were evaluated as the markers of oxidative stress, inflammation and apoptosis respectively.

Results: Both treatments had reduced the adriamycin induced cardiotoxicity. Whereas CAP treatment showed a better reduction of inflammation, superior preservation of posterior wall architecture and enhanced improvement in relative wall thickness when compared to CAR. Oxidative stress, caspase 3 activity and markers of myocyte damage were better recovered with CAR treatment while other parameters were found to be identically attenuated.

Conclusion: The present study found an identical therapeutic outcome from ACE inhibition and β blockade with a better attenuation of inflammation and structural preservation with ACE inhibition and superior antioxidant and antiapoptotic effect with βB treatment.

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1. Introduction

Adriamycin (ADR) is an anthracycline based antineoplastic agent which is used in the treatment of leukaemia, lymphomas, carcinomas and soft tissue sarcomas either alone or in combination with other chemotherapy regimens [1]. The cytotoxic effects of ADR are mediated by DNA intercalation and inhibition of the progression of the topoisomerase II, thereby relaxing the DNA supercoils preventing the transcription [2]. Common adverse effects of ADR include myelosuppression, oral mucositis, oesophagitis, hand-foot syndrome and liver dysfunction. The potent and life threatening adverse effect of ADR is cardiomyopathy induced heart failure with a rate of incidence about 4% with a dose of 500–550 mg/m^2, 18% with a dose is 551–600 mg/m^2 and 36% with a dose more than 600 mg/m^2 [3].

The mechanisms of ADR induced cardiomyopathy are not fully understood, but evidences indicate the involvement of oxidative stress and cardiac inflammation leading to apoptosis mediated structural deformation and its transition into failure [4,5]. Free radical generation by ADR in mitochondrial dependent and independent manner induces oxidative stress in the myocardium [6–8]. Treatment with various antioxidants has shown a promising recovery from the ADR induced cardiotoxicity in pre-clinical models [9,10] . But the clinical studies on utility of antioxidants in ADR cardiotoxicity, showed an inconsistent results due to multiple issues like bioavailability of the antioxidant, timing of therapy, type and degree of malignancy and other combinational

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antineoplastic drugs making them a failure in clinical setup [11]. Apart from this, ADR induces processing and release of interleukin-1β through activation of the NLRP3 inflammasome. This causes cardiac inflammation which further complicates the management of the disease [12]. The interdependency and ability of the inflammation and oxidative stress in initiation and progression of myocyte apoptosis can cause the transition into failure [13,14].

Dexarozaxone a chelating agent which is used in management of ADR induced cardiotoxicity is being restricted due to its possibility of higher rate of secondary malignancies and acute myelogenous leukemia in pediatric patients [15]. Presently, strategies that are employed in managing the heart failure are being used to treat ADR induced cardiotoxicity. Pulmonary and systemic venous congestion are usually relived with diuretics and systolic failure is corrected with β-Adrenergic blockers (βB) [16]. It was demonstrated that left ventricle diameters remained unaltered with improved diastolic function in patients receiving carvedilol in comparison with placebo control indicating the importance of βBs in treating ADR induced cardiotoxicity [17]. Nevertheless, no controlled studies were performed to define whether βBs can prevent progression of ADR induced cardiotoxicity with better clinical outcomes [16]. On the other hand administration of ACE inhibitors like zofenepril and captopril restored systolic function indicating the importance of angiotensin signaling in ADR induced cardiotoxicity [18–20]. In this situation, the lack of studies focussing on comparing the efficacies βBs and ACE inhibitors in modulating the ADR induced cardiotoxicity impedes us in crafting a superior guideline for pharmacological management.

Hence this study was designed to analyse and compare the pharmacological outcome of both βBs and ACE inhibitor in modulating the ADR induced cardiotoxicity. Pan adrenergic blocker Carvedilol (CAR) and ACE inhibitor Captopril (CAP) were employed in this study using a rodent model of ADR induced cardiotoxicity. Cardiovascular morphology, systolic and diastolic function were assessed by 2D transthoracic echocardiography. Myocyte damage was analysed by quantifying the circulating and myocardial cTnT and CkMB levels. Markers of oxidative stress, inflammation and apoptosis namely, myocardial lipid peroxidation, IL1β and caspase 3 activity were also analysed in the myocardium. Study highlighted that both the therapeutic strategies are more or less equipotent in preventing ADR induced cardiotoxicity, with a better anti-inflammatory effect and structural restoration by CAP and better antioxidant and anti-apoptotic effect by CAR treatment.

2. Materials and methods

2.1. Animals and study plan

The study was approved by institutional animal ethics committee (439/0/a/CPCSEA). Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines were adhered during the maintenance and experimentation. Male Wistar rats weighing between 150 and 200 g were procured from animal facility and maintained under standard environmental conditions and were fed with standard pellet diet with water supply ad libitum.

Thirty Two Male Wistar rats were randomly assigned into 4 groups each consisting of 8 rats.

1. Normal Saline group (NS) – received normal saline (0.5 ml) daily through oral gavage for 28 days.
2. Adriamycin group (ADR) – received single dose of ADR (10 mg/kg) as an I.V. bolus on day 1 and Normal saline 0.5 ml through oral gavage till the 28th day [21].
3. Captopril group (CAP) – received single dose of ADR (10 mg/kg) as an I.V. bolus on day 1 and received CAP (50 mg/kg) through oral gavage once daily for 28 days [22,20].
4. Carvedilol group (CAR) – received single dose of ADR (10 mg/kg) as an I.V bolus on day 1 and received CAR (10 mg/kg) through oral gavage once daily for 28 days [23,24].

2.2. Trans thoracic echocardiography (TTE)

After completion of the study, animals were anesthetized with sevoflurane (2%) and subjected echocardiographic evaluations using GE vivid 6 doppler echocardiography machine with 10 mHZ linear transducer [25,26]. Animals were placed in the left lateral decubitous position. Ejection fraction (EF) and percentage of left ventricular shortening or fractional shortening (FS), left ventricular internal diameter during diastole (LVIDD), left ventricular internal diameter during systole (LVISD), left ventricular posterior wall thickness during diastole (LVPWD), left ventricular posterior wall thickness during systole (LVPWS), interventricular septal wall thickness during systole (IVSS) and interventricular septal wall thickness during diastole (IVSD) were measured using M mode in both the short and long axis views according to the American Society of Echocardiography guidelines. Mitral diastolic inflow from the apical four chamber view was measured using Pulsed wave Doppler. Based on the curve of mitral diastolic flow, peak flow velocity (E) of early filling wave (E-wave), peak flow velocity (A) of atrial filling wave (A-wave), E/A ratio and Edt rate were determined. The M-mode and Doppler images were obtained at a speed of 150 mm/s. Data from three consecutive cardiac cycles was averaged for each measurement.

2.3. Sample collection and cardiac index calculation

Blood was collected from lateral tail vein and serum was prepared. The rats were then sacrificed and hearts were excised immediately, rinsed in ice-cold normal saline and sampled for further investigations. Tissue lysates were prepared by homogenising in RIPA buffer and incubated it on ice for 30 min followed by centrifugation at 5000*g* for 10 min at 40 °C. The supernatant of the myocardial lysate was used for the estimation of various biochemical parameters. Protein concentrations of samples were estimated by Bradford method.

2.4. Biochemical estimations

Myocardial lipid peroxidation was estimated by the method of Fraga et al [27]. Briefly, myocardial lysate was added to tricholoro acetic acid-thiobarbituric acid mixture and boiled for 20 min at 100 °C. The tubes were cooled and centrifuged at 1000 RPM for 5 min. Supernatant was collected and OD was read at 535 nm. Thiobarbituric acid reacting substances (TBARS) were quantified from the standard curve and normalised with protein content.

Cardiac troponin T (cTnT) levels in serum and myocardial lysate were estimated using commercial rat Cardiac troponin T assay kit, kamiya biomedical (Cat. No. KT-60845) as per manufacturer's guidelines.

Creatine kinase – MB activity levels in serum and myocardial lysate were estimated using Creatine kinase – MB assay kit, Agappe diagnostics (Cat. No. 11207004) as per manufacturer's guidelines.

Caspase 3 enzymatic activity assay was performed according to Varsha Kaushal et al using Ac-DEVD-ρNA as substrate [28]. The non-specific reactions were blocked by parallel reactions with inhibitor, Z-VAD-FMK. The amount of pNA cleaved and released by caspase 3 was quantified spectrophotometrically.

2.5. Statistical analysis

Data was expressed as mean $\pm$ SD. Data was analysed by one way ANOVA followed by Bonferroni post hoc test. $P < 0.05$ was considered to be significant.

3. Results

3.1. Effect of treatments on cardiac morphology

Both the treatments prevented the cardiomyopathic phenotype in the myocardium by preserving the cardiac architecture. The LV

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