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Effects of aliskiren on hemodynamic parametersin daunorubicin -induced acute cardiomyopathy in rats

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ABSTRACT

Daunorubicin ((DNR)) used in oncological practice against a wide variety of solid organ tumors and hematologic malignancies, including leukemia, lymphoma, breast cancer, lung cancer, multiple myeloma and sarcoma. however clinical use of this agent is limited due to cardiomyopathy and cardiac heart failure. one of the important player in the development of cardic hypertrophy and reperfusion injury is renin-angiotensin system. Aliskiren (ALK) a recent drug of a direct inhibitor of the renin enzyme. It Protect cardiomyopathy by the inhibition of the renin activity. Present study is towards the evaluation of protective effcets of ALK 50 and 100 mg/kg/day in rats. The systolic, diastolic, mean BP and heart rate were significantly (P< 0.01) increased in DNR control group as compared to normal control group. Thus the results provide clear evidence that the ALK pretreatment offered significant protection against DNR-induced Hemodynamic parameters changes.

Keywords: Daunorubicin, Cardiomyopathy, Aliskiren, Telmisartan and Hemodynamic parameters

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INTRODUCTION

Daunorubicin ((DNR)) has been used in oncological practice since the late 1960s. It is highly effective against a wide variety of solid organ tumors and hematologic malignancies, including leukemia, lymphoma, breast cancer, lung cancer, multiple myeloma and sarcoma[1]. The therapeutic use of this drug is restricted because of acute and chronic side effects especially in the heart and kidney. The acute side effects such as nausea, vomiting, sinus tachycardia and or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, as well as heart block have also been reported associated with it. But the chronic side effects represented by the development of left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm[2,3] .

The exact mechanism of daunorubicn induced cardiotoxicity are unclear however data accumulated to date indicates that anthracycline metabolism either through generation of free radicals or toxic metabolites, or a combination of both, is a significant contributor to the drugs' cardiotoxicity[4,5]. This novel concept of cardiomyocyte apoptosis has broader implications, especially with regard to myocardial function, because loss of cardiomyocytes could initiate or exacerbate heart failure. in this pathway suggests that the drug-sensitive cells clinically relevant concentrations of DNR trigger then generation of ROS that leads to a process and makes the initial ROS burst the rate-limiting step in DNR-induced apoptosis signaling for the primary apoptotic initiation step[6].

Many types of agents have been used to treat DNR-induced cardiomyopathy including Quercetin, Pomegranate, Nigella Sativa Oil, Carvedilol, Talmisartan[7,8,9,10]. But, all of these agents have pronounced clinical disadvantages, including a significant decline in HDL levels, an inability to prevent DNR-induced mortality and weight loss, and potentiation of DNR-induced myelosuppression. Numerous studies have suggested that angiotensin-converting enzyme inhibitors

and angiotensin receptor blockers (ARBs) have protective effects against anthracycline cardiotoxicity[11].

The exact causal mechanism of DNR-induced cardiomyopathy is not completely clear. however, various mechanisms have been attributed to DNR-induced cardiomyopath such as release of vasoactive amines, generation of reactive oxygen species (ROS), induction of apoptosis, oxidative DNA damage, lipid peroxidation, impairment of enzymatic activity of creatine kinase, and induction of renin angiotensin system (RAS) activity[12,13]. The principal player involved in daunorubicin induced toxicity appears to be iron that catalyses the production of highly toxic hydroxyl radicals. it is also found that anthracycline inhibit iron mobilization from storage protein ferritin, resulting in accumulation of iron within the cardiomyocytes. topoisomerase II inhibition and DNA intercalation considered to play in antineoplastic effects while iron catalysed increased formation of ROS in anthracycline induced cardiotoxicity[14,15].

Anthracycline chemotherapeutic drugs as for example daunorubicin, adriamycin induced cardiomyopathy by involvement of over activity of cardiac renin angiotensin system. As reported previously also that Angiotensin II plays a important key role in the process of Anthracycline induced cardiotoxicity. The angiotensin-converting enzyme inhibitor and angiotensin receptor blocker play exert a protective role towards Anthracycline induced cardiotoxicity[16,10,17].

A novel drug of renin angiotensin system inhibitors aliskiren is a direct inhibitor of the renin enzyme and cardioprotective against Anthracyclineinduced toxicity in heart and kidney. In another way the inhibition of the renin activity by aliskiren may suitable and promising approach in the protection of Anthracycline induced toxicity[18].

MATERIALS AND METHODS

Experimental animals

The study synopsis was approved by the Institutional Animal Ethics Committee (IAEC) of Jaipur National University, Jaipur Rajasthan. Albino rats of Wistar strain, with body weight 160–200 g were procured from Central Animal House Facility of Jaipur National University Jaipur and process under standard laboratory procedure conditions at 20–25 8C. The animals were kept in propylene cages under controlled conditions of illumination and had a free access to commercial pellet diet and water ad libitum.

Drugs and chemicals

Daunorubicin (Jubilant Life sciences limited Bhartiagram Gajraula, Distt. Amroha UP), aliskiren (Dabur India Ltd., Sahibabad, Uttra Pradesh, India) and Telmisartan (Glenmark Pharmaceutical Ltd., Kisanpura, Himachal Pradesh) were gratefully received for the study. Caspase-3 inhibitor assay kits from BioVision (USA), LDH and CK-MB assay kits from Reckon Diagnostics Ltd. (India), were purchased. All the other chemicals used were of analytical grade. HPLC grade water was used for all biochemical assays.

Experimental schedule

After acclimatization, all the animals were randomly allocated into six groups of eight animals each and treated as follows:

- Group I received physiological saline (0.5 mL/kg i.p., same schedule as group II) and served as control
- Group II received Daunorubicin four times a week in sixteen equal doses over a period of four weeks for a cumulative dose of 1.25 mg/kg, i.p.
- Groups III, IV, and V received 30 mg/kg ALK, 100 mg/kg ALK, 10 mg/kg Telmisartan respectively per day by oral for 42 days along with DNR (1.25 mg/kg, i.p.) as the same schedule as group II
- Group VI received 100 mg/kg aliskiren alone by gavage for 42 days.

After 24 h of last dose of DNR, the rats were anesthetized with ether for collection of blood samples from the tail vein. The hemodynamic parameters systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate were measured

Hemodynamic measurements

Biopac Non-Invasive Blood Pressure Recording Instrument was used for Hemodynamic measurements by tail cuff method. All the rats were initially examined in the restrainer for a time of 15 min every day about 15 days before to the day of measurement of the hemodynamic parameters such as systolic blood pressure, diastolic blood pressure, mean blood pressure and heart rate.

Data and statistical analysis

All results are expressed as mean standard error of mean (S.E.M.). Groups of data are compared with the analysis of variance (Anova) followed by Dunnett's t test to identify significance among groups. Values are considered statistically significant at $P < 0.05$.

RESULTS

Hemodynamic parameters

The systolic, diastolic, mean BP and heart rate were significantly ($P< 0.01$) increased by 23.6%, 22.45%, 22.5% and 23% respectively in DNR control group as compared to normal control group. However, ALK 30, ALK 50, ALK 100 and TEL 10 groups showed significant ($P< 0.01$) reduction in systolic (11.2%, 13.1%, 16.4% and 14.8% respectively), diastolic (9.2%, 11.5%, 16.0% and 14.0% respectively), mean arterial Pressure (10.05%, 12.14%, 16.16% and 14.34% respectively) and heart rate (9.2%, 12.4%, 16.8% and 15.4% respectively) as compared to DNR control group. Although, ALK 30 pretreated group did not show significant protection from rise in hemodynamic parameters as compared to DNR control group

TABLE 1:

Treatment regimen	Systolic BP (mm Hg)		Diastolic BP (mm Hg)		Mean arterial Pressure (mm Hg)		Heart rate (beats/min)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Control	138.36	137.20	91.51	93.65	107.11	108.43	346.61	351.90
DNR	137.12	169.55	95.06	114.68	108.97	132.83	345.82	432.84
ALK (30mg/kg) + DNR	138.08	150.56	91.44	104.13	106.89	119.48	345.31	393.02
ALK (50mg/kg) + DNR	137.85	147.51	94.4	101.49	108.77	116.71	355.60	379.17
ALK (100 mg/kg) + DNR	137.96	141.75	94.6	96.33	108.94	111.36	357.52	360.13
TEL (10mg/kg) + DNR	137.40	144.45	95.0	98.62	109.02	113.78	358.35	366.18
ALK (100 mg/kg)	137.5	124.82	93.84	88.62	108.28	100.5	348.44	340.01

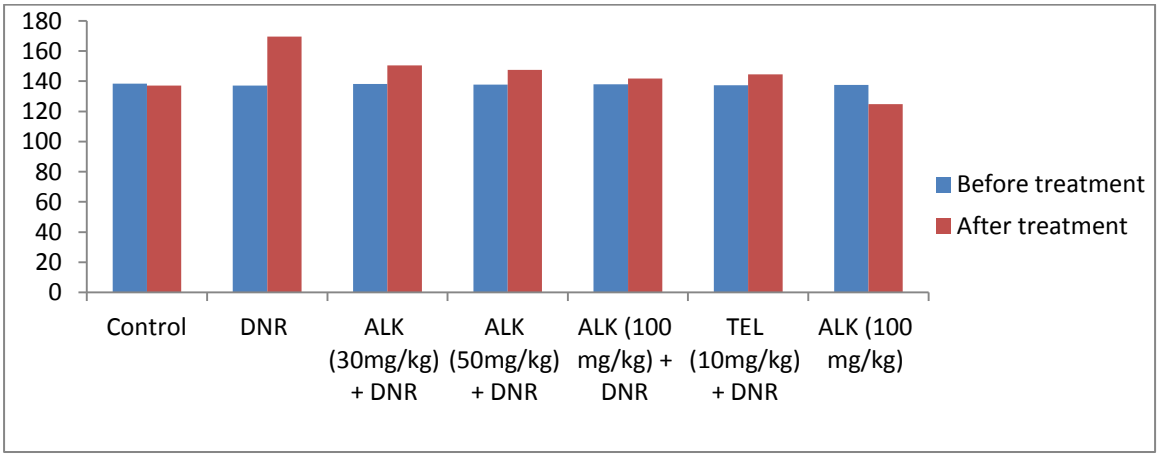

Figure 1: Systolic blood pressure Vs. Treatment regimen

Groups of data are compared with the analysis of variance (ANOVA) followed by Dunnett's t test.

Values are considered statistically significant at P < 0.05, p<0.01. DNR control compared with normal control group. p<0.01; All treated groups compared with DNR-control group

ALK per se group compared with normal control group

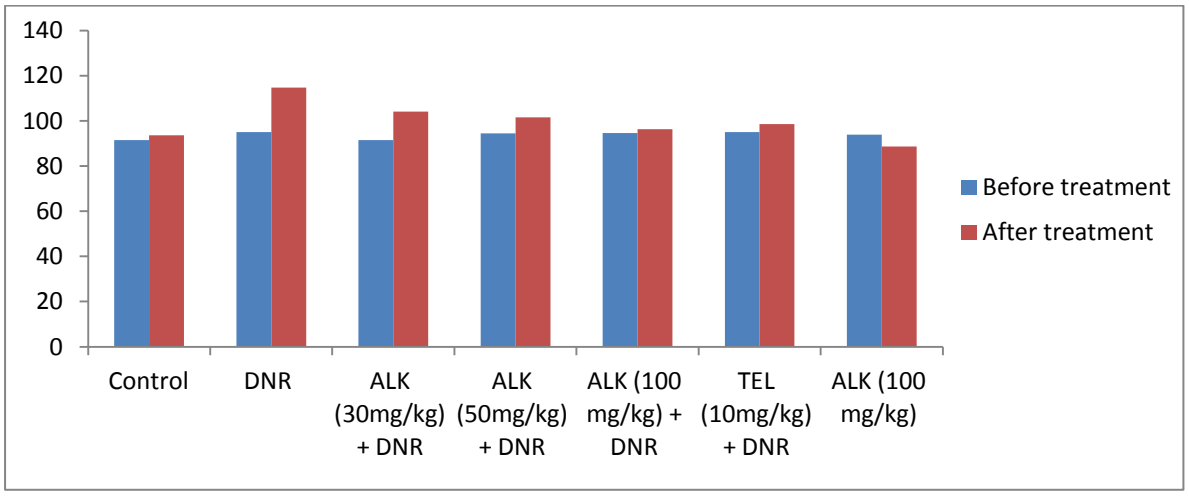

Figure 2: Diastolic blood pressure Vs. Treatment regimen

Groups of data are compared with the analysis of variance (ANOVA) followed by Dunnett's t test.

Values are considered statistically significant at P < 0.05. p<0.01; DNR control compared with normal control group. p<0.05, p<0.01; All treated groups compared with DNR-control group. ALK per se group compared with normal control group

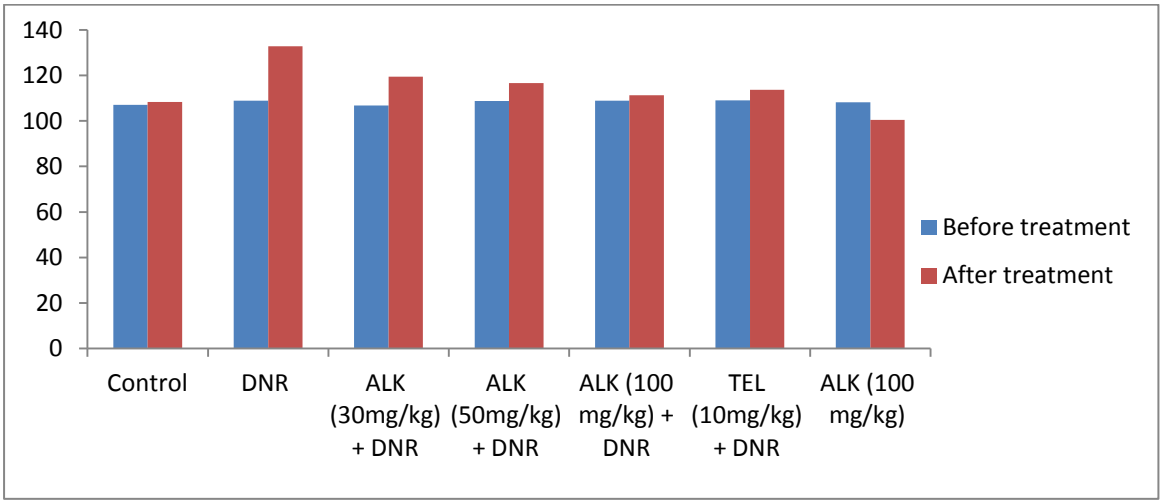

Figure 3: Mean arterial pressure Vs. Treatment regimen

Groups of data are compared with the analysis of variance (ANOVA) followed by Dunnett's t test.

Values are considered statistically significant at P < 0.05. ##p<0.01; DNR control compared with normal control group. p<0.01; All treated groups compared with DNR-control group. ALK per se group compared with normal control group

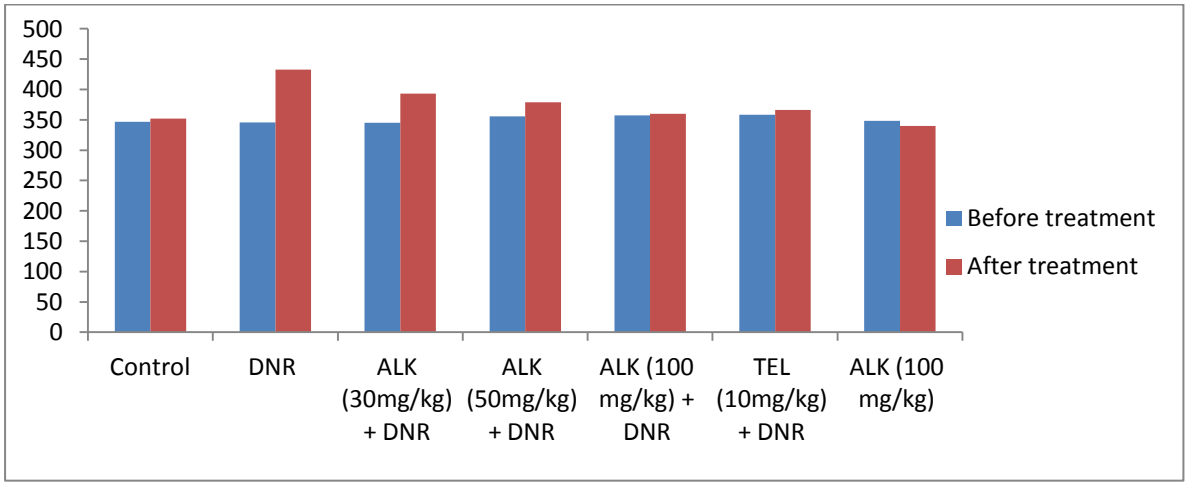

Figure 4: Heart rate Vs. Treatment regimen

Groups of data are compared with the analysis of variance (ANOVA) followed by Dunnett's t test.

Values are considered statistically significant at P < 0.05. p<0.01; DNR control compared with normal control group. p<0.01; All treated groups compared with DNR-control group

ALK per se group compared with normal control group

DISCUSSION

Daunorubicin is antibiotics belong to the anthracycline group widely used for for the treatment of cancer patients. The anticancer therapy with DNR is adversely limited by risks such as cardiomyopathy and congestive heart failure[1,19]. The pathogenesis of DNR-induced cardiomyopathy has not yet been fully clear but ongoing studies provides a good highlight to pathogenesis and give understanding to clear involvement of myocardial apoptosis and oxidative stress. In our findings we focused on studying the changes in apoptotic factor in terms of systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate. The results of our study have fined that a sixteen equal cumulative doses of DNR (1.25 mg/kg, i.p.) induces cardiomyopathy in rats, which is similar with the previous reported studies by other investigators[20,21]. DNR administration caused a significant increase (P < 0.01) in the blood pressure; systolic, diastolic and mean, as well as heart rate in the pathogenic control rats (DNR) as compared to Normal control group which is in continuation to that of previous studies[22,23]. The increase in mean BP and heart rate in pathogenic rats as compared to normal healthy control rats could be the result of increased release of renin and catecholamines that leads to formation of Ang I and finally Ang II[10]. ALK prevented the increase in heart rate and blood pressure in this study and showed encouragement in its use as a antihypertensive drug and widely accepted as a key regulator of cardiovascular and renal function and plays a major role in water and salt homeostasis and blood pressure control.

Through the inhibitory effect of renin activity by ALK in pretreatment significantly reduced systolic blood pressure, diastolic blood pressure, mean blood pressure and heart rate. TEL pretreatment significantly decrease systolic blood pressure, diastolic blood pressure, mean blood pressure and heart rate by blocking angiotensin 1 receptor. The higher dose of ALK in treated rats showed better protection than TEL pretreated rats which may be because of inhibition of plasma renin activity by ALK[24,25]. It was found that ALK 30 mg/kg, per day not effective in protecting DNR-induced

cardiomyocytes. This finding conclude that effect of ALK 30 is blocked by DNR induced reactive stimulation of the renin-angiotensin-aldosterone system and only higher dose of ALK could neutralize the renin-angiotensin-aldosterone system[26,27].

CONCLUSION

On the basis of our above investigation it is recommended that DNR-induced cardiomyopathy has RAS relationship. The results find also indicate that ALK pretreatment may be an complement to weaken the DXR-induced cardiac toxic effects. Further studies are needed to validate this conclusion and find out the affiliation between DNR-induced cardiomyopathy and RAS.

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