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Research Paper

Evaluation of the Cardioprotective Activity of Empagliflozin, Linagliptin and Their Combination Against Doxorubicin-Induced Cardiotoxicity in Rats

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ABSTRACT

Background Doxorubicin is an effective antineoplastic agent whose clinical application may be limited by cardiotoxicity. The present study was undertaken to evaluate the cardioprotective activity of empagliflozin and linagliptin, administered individually and in combination, against doxorubicin-induced cardiotoxicity in rats. Materials and Methods Healthy adult male Wistar rats weighing 180–225 g were used. Doxorubicin was administered intraperitoneally at 2.5 mg/kg in six equal doses on alternate days over two weeks, giving a cumulative dose of 15 mg/kg. Empagliflozin (10 mg/kg/day, orally) and linagliptin (5 mg/kg/day, orally) were administered for 15 days, either individually or in combination. Vitamin E (100 mg/kg, orally) was used as the standard treatment. Serum glucose, CK-MB, LDH, total cholesterol, triglycerides, HDL-C, LDL-C, VLDL-C and cardiac troponin I were evaluated. Histopathological examination of cardiac tissue was also performed. Results Doxorubicin-induced cardiotoxicity produced marked biochemical and histopathological alterations. CK-MB increased from 18.50 ± 1.190 U/L in the normal control group to 27.50 ± 1.443 U/L in the disease control group, while LDH increased from 175.00 ± 6.445 to 220.00 ± 12.25 U/L. Treatment with empagliflozin, linagliptin and their combination reduced reported CK-MB levels to 21.50 ± 1.323 , 23.50 ± 1.190 and 19.75 ± 0.8539 U/L, respectively. Cardiac troponin I was 4.50 ng/mL in the disease control group and was reported as 3.11, 2.67 and 2.01 ng/mL in the empagliflozin, linagliptin and combination groups, respectively. Conclusion The present findings indicate that empagliflozin and linagliptin individually attenuated selected biochemical and histopathological alterations associated with doxorubicin-induced cardiotoxicity. Further mechanistic and functional studies are required to establish the mechanisms underlying these observations.

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INTRODUCTION

Doxorubicin is an anthracycline anticancer drug widely used in the treatment of various malignant conditions. Its therapeutic application is associated with the risk of cardiac injury, which may limit its clinical utility.¹ Experimental doxorubicin-induced cardiotoxicity provides a useful model for evaluating potential cardioprotective interventions.²

Cardiac injury can be assessed using biochemical biomarkers and histopathological examination.³ CK-MB and LDH are commonly evaluated biochemical indicators associated with myocardial injury, whereas cardiac troponin I provides a more specific marker of cardiomyocyte injury.^{4,5} Histological examination provides complementary information regarding structural alterations in cardiac tissue.⁶

Empagliflozin is a sodium-glucose cotransporter-2 inhibitor primarily used in the management of type 2 diabetes mellitus.^{7,8} Linagliptin is a dipeptidyl peptidase-4 inhibitor used for glycaemic management.⁹⁻¹¹ The present study was designed to evaluate the effects of these agents in an experimental model of doxorubicin-induced cardiotoxicity.

The objectives were to evaluate the cardioprotective activity of empagliflozin and linagliptin, assess serum CK-MB, glucose and LDH, investigate changes in lipid-profile parameters, compare the effects of the individual drugs with their combination.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Healthy adult male Wistar rats weighing approximately 180–225 g were used. Animals were housed in polypropylene cages under controlled laboratory conditions, including approximately 24°C temperature, a 12-hour

light/dark cycle and 35–60% humidity. Pellet food and filtered water were provided ad libitum.

2.2 Experimental Design

After one week of acclimatization, the animals were divided into six groups, with six animals in each group (n=6). The treatment duration was 15 days.

Group	Treatment
I	Normal control – vehicle
II	Disease control – doxorubicin-induced cardiotoxicity
III	Vitamin E standard – 100 mg/kg p.o.
IV	Empagliflozin – 10 mg/kg/day p.o.
V	Linagliptin – 5 mg/kg/day p.o.
VI	Empagliflozin 10 mg/kg/day + Linagliptin 5 mg/kg/day p.o.

The treatment groups received the respective treatments followed by doxorubicin administration according to the experimental protocol.

2.3 Induction of Doxorubicin-Induced Cardiotoxicity

Doxorubicin was administered intraperitoneally at a dose of 2.5 mg/kg in six equal doses on alternate days over two weeks, giving a total cumulative dose of 15 mg/kg body weight. Blood samples were collected at the conclusion of treatment and hearts were collected for histopathological examination.

2.4 Biochemical Analysis

Serum glucose, total cholesterol, LDH, HDL-C and VLDL-C were assessed using commercial diagnostic kits. Serum triglycerides were estimated using a diagnostic kit, while CK-MB and cardiac troponin I were quantitatively evaluated using appropriate diagnostic assays.

2.6 Statistical Analysis



The experimental values were expressed as mean $\pm$ SEM. One-way ANOVA was used to assess differences among groups, followed by additional statistical tests as described in the thesis methodology.

3. Results

3.1 Effect on Serum Glucose, CK-MB and LDH

The results of serum glucose, CK-MB and LDH are presented in Table 1.

Table 1. Effect of empagliflozin, linagliptin and their combination on serum glucose, CK-MB and LDH

Group	Treatment	Glucose (mg/dL) Mean $\pm$ SEM	CK-MB (U/L) Mean $\pm$ SEM	LDH (U/L) Mean $\pm$ SEM
I	Normal control	100.50 $\pm$ 7.030	18.50 $\pm$ 1.190	175.00 $\pm$ 6.445
II	Disease control	82.00 $\pm$ 3.136	27.50 $\pm$ 1.443	220.00 $\pm$ 12.25
III	Empagliflozin	97.60 $\pm$ 9.772	21.50 $\pm$ 1.323	198.75 $\pm$ 3.227
IV	Linagliptin	96.25 $\pm$ 10.06	23.50 $\pm$ 1.190	190.50 $\pm$ 2.630
V	Empagliflozin + Linagliptin	90.06 $\pm$ 4.262	19.75 $\pm$ 0.8539	196.00 $\pm$ 2.739
VI	Vitamin E standard	90.54 $\pm$ 2.123	18.75 $\pm$ 0.451	178.45 $\pm$ 1.323

The normal control group showed a serum glucose level of 100.50 $\pm$ 7.030 mg/dL, whereas the disease control group showed 82.00 $\pm$ 3.136 mg/dL. Empagliflozin, linagliptin and the combination produced reported glucose values of 97.60 $\pm$ 9.772, 96.25 $\pm$ 10.06 and 90.06 $\pm$ 4.262 mg/dL, respectively.

3.2 Effect on Serum Lipid Profile

The lipid profile included total cholesterol, triglycerides, HDL-C, LDL-C and VLDL-C.

Table 2. Effect of treatments on serum lipid profile

Group	TC (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	VLDL-C (mg/dL)
I. Normal control	103.50 $\pm$ 14.01	49.50 $\pm$ 2.102	20.50 $\pm$ 2.102	86.75 $\pm$ 1.702	20.50 $\pm$ 2.104
II. Disease control	203.50 $\pm$ 14.01	178.00 $\pm$ 24.01	35.25 $\pm$ 2.056	160.50 $\pm$ 2.46	35.83 $\pm$ 2.227
III. Empagliflozin	151.80 $\pm$ 8.64	96.25 $\pm$ 6.169	26.25 $\pm$ 3.119	146.80 $\pm$ 2.68	26.25 $\pm$ 3.595
IV. Linagliptin	132.80 $\pm$ 6.42	59.58 $\pm$ 1.530	25.00 $\pm$ 2.041	146.80 $\pm$ 2.68	25.00 $\pm$ 2.232
V. Empagliflozin + Linagliptin	122.00 $\pm$ 7.450	47.84 $\pm$ 1.295	23.00 $\pm$ 2.852	139.30 $\pm$ 2.83	23.00 $\pm$ 2.078
VI. Vitamin E standard	121.00 $\pm$ 5.342	46.26 $\pm$ 2.234	21.30 $\pm$ 4.552	130.20 $\pm$ 3.23	21.40 $\pm$ 2.415

The disease control group showed higher reported total cholesterol, triglycerides, LDL-C and VLDL-C than the normal control group. Total cholesterol increased from 103.50 $\pm$ 14.01 mg/dL in the normal control group to 203.50 $\pm$ 14.01 mg/dL in the disease control group.

Treatment with empagliflozin, linagliptin and their combination resulted in lower reported total cholesterol, triglycerides, LDL-C and VLDL-C compared with the disease control group. Among the test-treatment groups, the combination group



demonstrated the lowest reported total cholesterol, triglyceride, LDL-C and VLDL-C values.

The HDL-C value in the combination group was 23.00 ± 2.852 mg/dL, compared with 26.25

± 3.119 mg/dL in the empagliflozin group and 25.00 ± 2.041 mg/dL in the linagliptin group.

3.3 Effect on Cardiac Troponin I

Cardiac troponin I was assessed as a biochemical marker of myocardial injury.

Table 3. Effect of treatments on cardiac troponin I

Group	Treatment	Troponin I (ng/mL)
I	Normal control	1.50
II	Disease control	4.50
III	Vitamin E standard	0.80
IV	Empagliflozin	3.11
V	Linagliptin	2.67
VI	Empagliflozin + Linagliptin	2.01

The disease control group showed an increase in cardiac troponin I to 4.50 ng/mL compared with 1.50 ng/mL in the normal control group. The reported values were 3.11 ng/mL for empagliflozin, 2.67 ng/mL for linagliptin and 2.01 ng/mL for the combination treatment. Thus, the combination group showed a lower reported troponin I value than either individual treatment group.

DISCUSSION

The present study evaluated the cardioprotective potential of empagliflozin, linagliptin and their combination in a rat model of doxorubicin-induced cardiotoxicity. Doxorubicin was administered at 2.5 mg/kg intraperitoneally in six equal alternate-day doses over two weeks, resulting in a cumulative dose of 15 mg/kg.

The disease control group demonstrated increased CK-MB and LDH compared with the normal control group. CK-MB and LDH are biochemical indicators that may increase following tissue injury, while cardiac troponin I is a more specific indicator of cardiomyocyte injury. The biochemical findings were supported by histopathological examination, in which the disease control group showed the highest degree of cardiac necrosis.

Empagliflozin treatment reduced the reported CK-MB value from 27.50 ± 1.443 U/L in the disease control group to 21.50 ± 1.323 U/L. It also produced lower reported total cholesterol, triglyceride and VLDL-C values than the disease control group. Histopathological examination showed less cardiac necrosis in the empagliflozin-treated group.

Linagliptin treatment similarly reduced the reported CK-MB value compared with the disease control group. Lower reported total cholesterol, triglyceride and VLDL-C values were also observed. Histopathological examination demonstrated less cardiac necrosis than in the disease control group.

Direct comparison of the individual treatments showed CK-MB values of 21.50 ± 1.323 U/L for empagliflozin and 23.50 ± 1.190 U/L for linagliptin, compared with 27.50 ± 1.443 U/L in the disease control group.

The combination of empagliflozin and linagliptin produced a CK-MB value of 19.75 ± 0.8539 U/L, lower than the values observed with either individual treatment. The combination also demonstrated the lowest reported total cholesterol, triglyceride, LDL-C and VLDL-C values among the test-treatment groups. The lipid findings showed marked increases in total cholesterol, triglycerides, LDL-C and VLDL-C in the disease



control group compared with the normal control group. The combination group demonstrated the lowest reported total cholesterol and triglyceride values among the test-treatment groups.

The HDL-C findings require cautious interpretation because the combination group had a lower reported HDL-C value than both individual treatment groups. Therefore, no beneficial conclusion should be drawn from HDL-C alone.

Taken together, the biochemical and histopathological findings provide complementary evidence that treatment with empagliflozin, linagliptin and their combination was associated with attenuation of selected manifestations of doxorubicin-induced cardiac injury. The combination treatment showed favourable findings in several parameters; however, the present data do not establish a synergistic interaction between the two drugs. Confirmation of synergy would require an appropriate factorial experimental design and dedicated interaction analysis.

CONCLUSION

The present experimental study showed that doxorubicin administration produced biochemical and histopathological alterations consistent with cardiac injury in rats.

Empagliflozin and linagliptin individually reduced selected cardiac injury biomarkers and were associated with reduced cardiac necrosis compared with the disease control group. The combination of empagliflozin and linagliptin demonstrated favourable findings across several evaluated parameters, including CK-MB, lipid profile and cardiac histopathology.

The combination treatment showed a reported CK-MB value of 19.75 ± 0.8539 U/L and less cardiac necrosis than either individual treatment. These findings support further investigation of empagliflozin and linagliptin, individually and in

combination, as potential cardioprotective interventions in experimental doxorubicin-induced cardiotoxicity.

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