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Levocetirizine and Amlodipine Restores Hepato-Cardiac Function in the Forced Swim-Induced Cardiac Remodelling Rat Model

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Authors' contributions

This work was carried out in collaboration between all authors. Authors FA, ALM and FAA designed the study. Authors AO, SS and KM performed the statistical analysis, wrote the protocol and first draft of the manuscript. Authors KM, AO and TJK managed the analyses of the study and performed experiments. Authors AO and KM managed the literature search. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Drug combination studies are of keen interest, especially to the clinician who encounters patients with multiple disease symptoms. In our study, we tried to assess the toxic/beneficial effect of a prominent calcium channel blocker–Amlodipine, when administered with Levocetirizine–an antihistamine drug, in forced swim-induced stress model of Albino Wistar Rats.
Methodology: Animals were subjected to forced swim-induced stress (FSIS) for remodelling in heart followed by Amlodipine (3 mg/kg/day) and Levocetirizine (0.5 mg/kg/day) treatment. Biochemical parameters like serum alkaline phosphatase, alanine transaminase, triglyceride, uric

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acid, serum amylase, sodium, potassium, calcium and total protein were assessed in serum samples. The modulations in cellular architecture were studied by heart and liver histopathology.
Results: The overall alteration in alkaline phosphatase, alanine transaminase, triglyceride, and uric acid significantly demonstrated the protective role of this drug combination in the stress-induced remodelling of the heart. Elevated levels of alkaline phosphatase and alanine transaminase were observed in the single-drug therapeutic groups ($P < 0.05$). The combination therapy restored the biochemical parameters, revealing the synergistic effect. A similar trend of change was observed in the levels of amylase ($P < 0.01$). In support of the serological findings, our histopathology results revealed FSIS-Amlo Levo group demonstrated near to normal cellular architecture with less fat depositions when compared to FSIS-Amlo and FSIS-Levo.
Conclusion: The combination therapy of these drugs demonstrated a significant beneficial effect on stress-induced cardiac remodelling under the given set of conditions.

Keywords: Amlodipine; levocetirizine; stress; combination therapy; cardiac remodelling.

1. INTRODUCTION

In hypertensive patients, expansion of ventricular infract often complicates the initial course of acute myocardial infarction. Ventricular dilatation, infarct thinning and progressive dysfunction are followed by the extensive collagenous scar tissues forming in the infarct zone [1]. Consequently, the shape of left ventricular chamber continues to distort in non-infarct areas and eccentric hypertrophy is also induced. All these changes in the cardiac morphology are collectively termed as 'cardiac remodelling' [2], leading to congestive heart failure and cardiac rupture (an aneurysm) [3]. The suppression of early ventricular infarct expansion and reversing cardiac remodelling by adjuvant pharmacological therapies are of immense interest since these complications of myocardial infarction remain significant determinants of morbidity and mortality.

In fact, it is likely that at the time of acute myocardial infarction or in the peri-infarction period for treatment of hypertension or post-infarction angina, patients may already be on the dose of calcium channel blockers (CCB) [4], notably, on Amlodipine-a long-acting dihydropyridine third-generation CCB. Levocetirizine-an antihistamine drug is commonly used to treat the allergies and hives. However, latest findings have revealed that its efficacy is not only limited to the treatment of allergies as it has shown to possess significant renoprotective and vasculoprotective effects [5] and also inhibits eosinophil adhesion to vascular cell adhesion molecule-1 under flow conditions [6]. However, no study reported the synergistic therapeutic impact or the toxicological outcomes of Amlodipine, when administered in combination with Levocetirizine. On the other hand, there are studies which state that H1-antihistamines may cause potentially fatal cardiac arrhythmias [7]. Indeed, biochemical and toxicological evaluation of Levocetirizine in the treatment of stress-induced hypertensive rats is a novel approach in the field of chemotherapy. This study aids in understanding the synergistic action of both the drugs in the stress-induced remodelled heart.

In the present study, a non-conventional approach was employed, where the alterations in liver parameters have been investigated in cardiac remodelled Albino Wistar Rats on the administration of Levocetirizine and Amlodipine in combination. In the previous studies, researchers have deciphered many relations between heart and liver. Interestingly, beyond doubt, it was proved that heart and liver are intimately correlated. The manifestation of the liver is well reported in a patient with heart ailments [8]. It is well established that sudden elevation of serum transaminase can lead to cardiac shock, and any alteration in liver function test can alter the electrophysiology of heart and its function [9]. The liver is one of the primary recipients of the cardiac output as nearly 25% of the volume of the blood moves towards its direction and any alteration in cardiac function can result in liver damage due to cut-off in the blood supply to it [10]. Moreover, liver damage also influences prognosis and output of cardiac diseases [9]. Diabetes, obesity, and hyperlipidaemia are associated with cardiac remodelling, and such conditions can intensify the susceptibility of the liver to the ischaemia reperfusion injury [11]. Additionally, abrupt fluctuation of aminotransferase and lactate dehydrogenase is related to hepatitis [12]. A considerable number of systemic diseases and chronic alcoholism affect both the liver and the

heart. This may have significant implications since the biochemical reactions in the heart and the liver orchestrate during surgical procedures [13].

Liver dysfunction is associated with heart malfunction and is generally without the symptoms. Jaundice, dependent oedema, and hepatomegaly with hepatojugular reflux are certain signs in a patient with tricuspid valve regurgitation [14]. Cholestasis is often linked to the complexity of heart remodelling, assumes prognostic relevance as increased serum alkaline phosphatase and bilirubin, the marker of cholestasis, predict all-cause mortality, cardiovascular death or hospitalization for heart failure. Chronic liver congestion also leads to synthetic function impairment, as shown by prolonged prothrombin time and reduced serum albumin concentration, which is also associated with all-cause mortality in patients with a reduced ejection fraction [9]. Moreover, chronic constrictive pericarditis is an association between the sustained elevation of systemic venous pressure and severe liver damage [15].

2. METHODOLOGY

2.1 Animals

The Albino-Wistar Rats (n=30; weight=100–120 grams; male) were obtained from King Fahad Medical Research Centre (KSA, Jeddah). They were acclimatized to three minutes of handling daily for initial seven days before the start of the experiment. All the rats were accommodated at animal-house of Biochemistry Department; Faculty of Science, King Abdulaziz University (KAU) at 21 ± 1°C temperature, relative humidity (60 ± 10%) on a 12-hour light/dark cycle with free access to food and water. The experimental procedures were as per the KAU Research Ethics Committee guidelines which are in compliance with the National Commission on the Ethics of Scientific Research at King Abdulaziz City for Science and Technology.

2.2 Forced Swim-induced Stress and Drug Administration

After initial handling, rats were randomly assigned to one of the five groups with six rats in each group which underwent 90 days of one of the five different treatments. The first group, i.e., normal control (n = 6) received a daily gavage of 1 ml/kg of distilled water. The second group, i.e., forced swim-induced stress (FSIS) control received a daily gavage of distilled water. Immediately after that, they were subjected to one trial per day of forced swim stress. The third group, i.e., forced swim-induced stress+Amlodipine (FSIS-Amlo) received a daily gavage of Amlodipine (Julphar, Gulf Pharmaceuticals Industries, Ras Al Khaimah, U.A.E), 3 mg/kg diluted in distilled water followed by FSIS. The fourth group, i.e., forced swim-induced stress+ Levocetirizine (FSIS-Levo) received gavage of Levocetirizine 0.5 mg/kg/day diluted in distilled water (Jamjoom Pharmaceuticals Co., Jeddah, Saudi Arabia) immediately after drug administration they were made to swim forcefully. The fifth group, i.e., forced swim-induced stress+ Amlodipine+ Levocetirizine (FSIS-AmloLevo) received a daily gavage of Amlodipine (3 mg/kg/day) and Levocetirizine (0.5 mg/kg/day) diluted in distilled water and subjected to FSIS after administration of the dosage.

The forced swim-induced stress (FSIS) was carried out in a clear and transparent cylinder (50 cm tall; 25 cm in diameter) filled to a level of 30 cm from the bottom with tap-water maintained at ~24°C. The rats were individually forced to swim for fifteen minutes; then they were taken out from the cylinder, dried and returned to their home cages. The aforementioned procedure is a modified method of Darrell D. Belke [16]. Prolonged exercise is associated with favourable cardiac remodelling leading to physiological hypertrophy [17]. In previous studies, satisfactory results were obtained with the administration of Amlodipine at 3 mg/kg/day [18,19], whereas, for Levocetirizine, a recent study by Anbar et al. [5] was made basis to standardize the dose.

At the end of the dosing and treatment period, rats of all the groups were sacrificed; blood-serum and the tissues, i.e., heart and liver were collected for the estimation of different biochemical parameters and histopathological examinations, respectively.

2.3 Determination of Biochemical Parameters

Before the sacrifice, on the 90th night, all the rats were kept for 12 hours of fasting and sacrificed on the next day under mild anaesthesia (Pentobarbital 40 mg/kg IP). Later on, the blood samples were drawn out from all the rats, via retro-orbital puncture technique as per the ethical committee norms and blood was collected in

anticoagulant tubes; collected blood was centrifuged at 4500 rpm and stored at 4°C. It is to be mentioned that serum samples were examined on the same day for the biochemical parameters. The serum alkaline phosphatase (SALP), triglyceride (TGL), alanine transaminase (ALT), uric acid, lactate amylase (AMY), total protein(TP), calcium (Ca) sodium (Na), and potassium (K) were determined using enzymatic methods on automated analyzer (Dimension-Clinical Chemistry System, USA) [20,21].

2.4 Histopathology

After the blood collection, heart and liver were isolated for histopathological analysis. The organs were fixed in 10% natural buffered formalin, dehydrated by passing through a graded series of alcohol and paraffin infiltration. The tissue slices of 5 µm sections were prepared using a semi-automated rotatory microtome and then it was dried at 37°C overnight. Hematoxylin and eosin were used for staining and observed under a magnification of 40x [22].

2.5 Statistical Analysis

All the experiments were performed in triplicate, and the data are expressed as mean ± SEM. One-way analysis of variance (ANOVA) was performed using GraphPad Prism 6 (Graph Pad Software, SanDiego, USA) to compare the differences. Dunnett's multiple comparisons test was also applied to compare different groups that are FSIS versus normal control, FSIS-Amlo, FSIS-Levo and FSIS-AmloLevo. 'P' values of different biochemical parameters were considered to be increasingly significant in the following order <0.05(*),<0.01(**) and < 0.001(***).

3. RESULTS

The alkaline phosphatase, alanine amino transferase, triglycerides, uric acid and amylase levels of various groups under forced swim-induced stress is depicted in Fig. 1. The mean ± SEM of specific groups and *P* values for significance of variance analysis are given in parenthesis wherever applicable.

3.1 Serum Alkaline Phosphatase (SALP)

FSIS-Levo (186 ± 7.5 U/L) and FSIS-Amlo (181 ± 12 U/L) groups exhibited significant increase ($P < 0.05$) in SALP levels as compared to FSIS control (97 ± 20 U/L); whereas, the FSIS-AmloLevo group showed normal values when compared to FSIS-control group. The mean ± SEM of normal control and FSIS Amlo-Levo was 102 ± 20 U/L and 85 ± 6.5 U/L, respectively.

3.2 Alanine Aminotransferase (ALT/SGPT)

The level of alanine aminotransferase/serum glutamic-pyruvic transaminase was significantly ($P < 0.05$) increased in FSIS-Levo group rats (94 ± 12 U/L) when compared to FSIS control group (58 ± 1.0 U/L). FSIS-Amlo (87 ± 14 U/L) and FSIS- AmloLevo group (61 ± 7.1 U/L) ALT levels were observed relatively lowered values.

3.3 Serum Triglycerides (TGL)

In the forced swim-induced stress group increased the level of triglycerides is observed (79 ± 6.9 mg/dL). FSIS-Levo (41 ± 1.0 mg/dL) and FSIS-AmloLevo (41 ± 4.8 mg/dL) treated groups' rats exhibited significant decreased values ($P < 0.05$ and $P < 0.01$, respectively) of serum triglycerides levels as compared to FSIS control.

3.4 Uric Acid (URCA)

Increased level of uric acid was exhibited by FSIS control group (2.1 ± 0.15 mg/dL). Highly significant ($P < 0.001$) decreased in the uric acid levels of FSIS-Levo (1.0 ± 0.0 mg/dL) and FSIS-Amlo (0.85 ± 0.15 mg/dL) groups were observed. Whereas the FSIS-AmloLevo group (1.9 ± 0.12 mg/dL) revealed the high level of uric acid near equivalent to the levels of FSIS control group.

3.5 Amylase (AMY)

FSIS-Levo (1054 ± 45 U/L) and FSIS-Amlo (1060 ± 30 U/L) groups exhibited significant increase ($P < 0.01$) in amylase levels as compared to FSIS control group; on the other hand, FSIS-AmloLevo group (664 ± 51 U/L) showed significant decrease ($P < 0.05$) in the amylase levels when compared to FSIS control group.

3.6 Ions

Serum ions like calcium, sodium, potassium and chloride were observed with stable levels in all the groups regardless of treatment. Restoration of these ions is perhaps due to trans-cellular distribution control of these ions and its excretion regulation by the renal system.

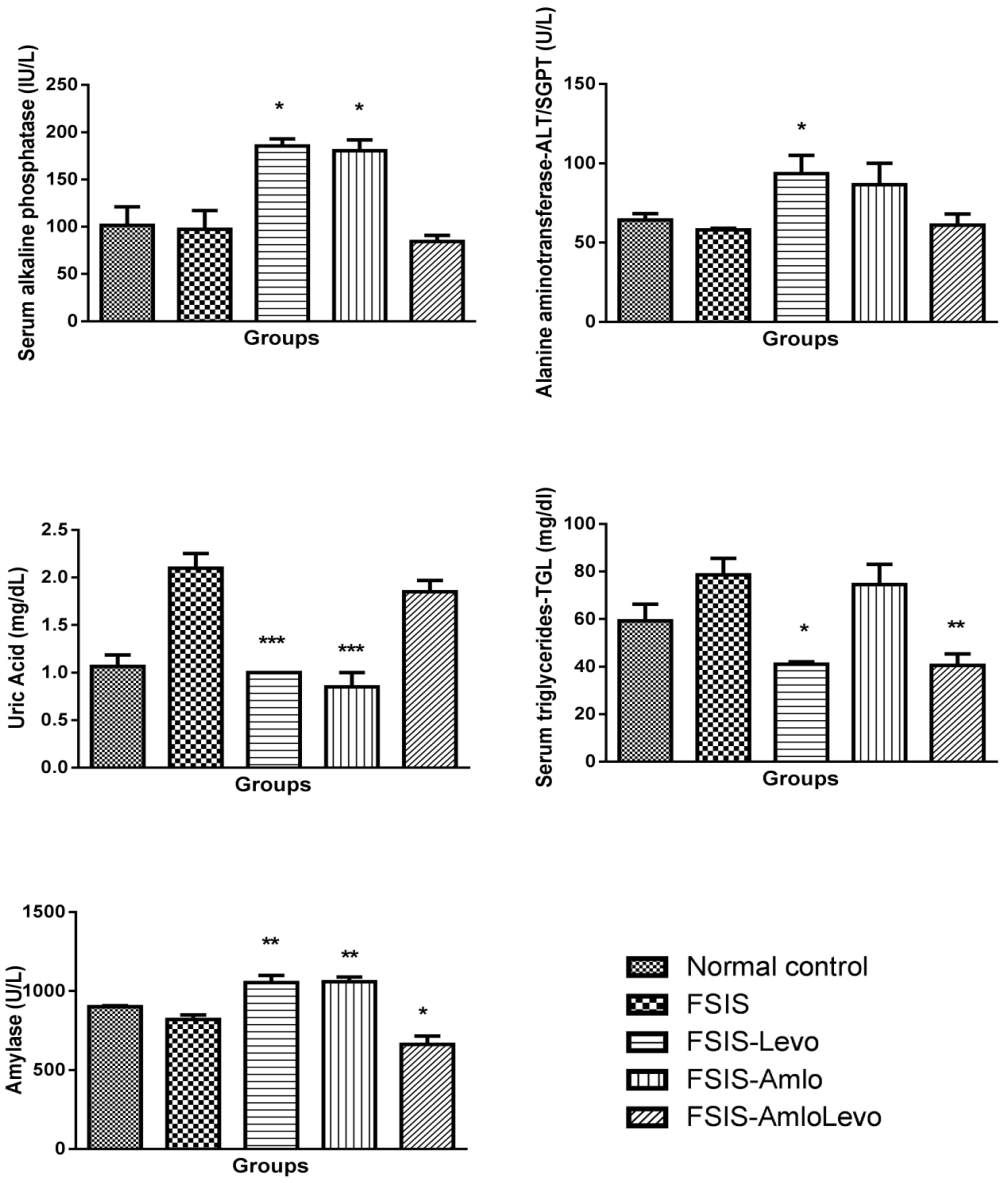

Fig. 1. Effect of Amlodipine and Levocetirizine on alkaline phosphatase, alanine aminotransferase, triglycerides, uric acid and amylase levels of different treated groups' rats under forced swim-induced stress (FSIS); treated groups are compared to FSIS control rats; values are mean ± SEM; n = 6; <0.05(*), < 0.01(**) and < 0.001(***)

3.7 Effect of FSIS-AmloLevo Treatment on Heart Histopathology

Fig. 2A depicts the normal cardiac cellular architecture with tight tissues, less fat deposition and perfect cellular arrangement with no interstitial spaces. Forced swim-induced hypertensive rats showed high interstitial spaces and distorted intercalated disc (Fig. 2B). FSIS-Levo treated group histopathology showed decreased interstitial space (Fig. 2C). FSIS-Amlo treated group showed the normal heart histopathology with stratified cellular architecture (Fig. 2D). FSIS-AmloLevo demonstrated the histopathology like the normal control with the less irregular distribution of eosinophils and slight fat deposits (Fig. 2E).

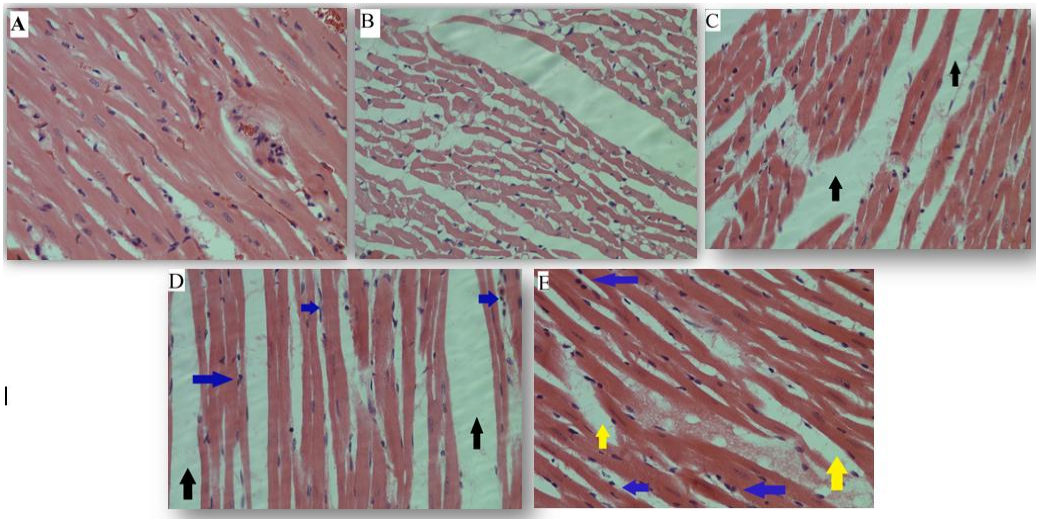

Fig. 2. Effect of Amlodipine-Levocetirizine combination on heart in different groups of rats: (A) Normal control: Normal control group shows normal histopathology of the heart there are no changes in cellular structure and intercalated disc. (B) FSIS control: Stress control histopathology shows distorted cellular architecture with increased interstitial space (C) FSIS-Levo: Tested drug histopathology shows decreased interstitial space (Black Arrows) (D) FSIS-Amlo Treated: Amlodipine treated group shows the normal heart histopathology with stratified cellular architecture. (E) FSIS-AmloLevo: demonstrating irregular distribution of eosinophils (Blue arrows) and having slight fat deposits (yellow arrows). H&E stained. The above picture for each group was chosen randomly. Original magnifications 40X

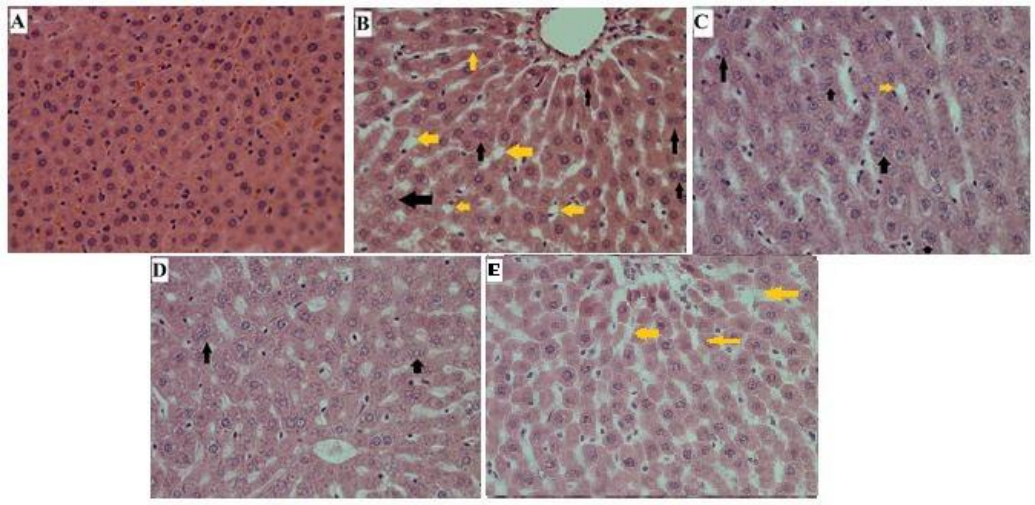

Fig. 3. Effect of Amlodipine-Levocetirizine combination on liver in different groups of rats: (A) Normal control: Normal control group shows normal histopathology of the liver, the cellular structure is intact with all normal features (B) FSIS control: Stress control histopathology shows distorted binucleated cellular architecture (black arrows) with increased fat depositions (yellow arrows) and (C) FSIS-Levo: Tested drug histopathology shows decreased binucleated cellular architecture (black arrows) with very less fat depositions (yellow arrows) (D) FSIS-Amlo Treated: Amlodipine treated group shows the normal liver histopathology few binucleated hepatic cells. (E) FSIS-AmloLevo: demonstrating near to normal cellular architecture with less fat depositions (yellow arrows) when compared to (C) and (D). The above picture for each group was chosen randomly. Original magnifications 40X H&E stained

3.8 Effect of FSIS-AmloLevo Treatment on Liver Histopathology

The normal hepatic cellular architecture was exhibited by group A (Fig. 3A). Forced swim-induced hypertensive rats showed binucleated small dark cytoplasm and unsystematic hepatic parenchyma with thick cord and huge fat deposits (Fig. 3B). FSIS-Levo treated group showed decreased binucleated cellular architecture with very less fat depositions (Fig. 3C). FSIS-Amlo treated group showed the normal liver histopathology with few binucleated irregular hepatic cells (Fig. 3D). FSIS-AmloLevo demonstrated increased fat depositions as compared to FSIS-Levo and FSIS-Amlo.

4. DISCUSSION

Myocardial infarction is instigated by myocardial ischemia due to increased lipid peroxidation [23], activation of pro-inflammatory reactions [24], excessive production of reactive oxygen species (ROS) [25]. There are several risk factors linked with the development of myocardial infarction, such as hypertension, dyslipidemia, diabetes, obesity, smoking etc. [26]. There is strong evidence from the recent studies that hypertensive patients have a higher risk of cardiovascular diseases [27]. In the current study, forced-swim-induced stress was given to various rat-groups, and the synergistic effect of Amlodipine and Levocetirizine was studied. Stress manifests itself as behavioural alterations, biochemical changes and physiological variations. Intense or chronic stress would lead to the well-known stress-related diseases such as hypertension, diabetes, stroke, cancer and depression [28-30].

Significant alterations in the level of uric acid, ALT, ALP and amylase were observed in the current study which was normalized by the combinational therapy exhibiting its synergistic effect. It is well-known that uric acid is the end product of purine metabolism. In most patients, the pathological alterations of the serum-uric acid results in serious clinical implications. It is useful in diagnosing the majority of the purine metabolic disorders. Recent studies implicate the decreased levels of uric acid when administered with calcium channel blockers like Amlodipine and Cilnidipine [31,32] by increasing the excretion of nitrogen monoxide. Interestingly, small variations in the total protein levels were found among the different therapeutic groups. Moreover, ions like sodium, potassium, chloride and calcium were also stable and unaffected by the drug treatment. This could be perhaps due to the trans-cellular distribution control of these ions and its excretion, regulated by the kidney [33-35].

In a recent study, researchers revealed the cetirizine-induced liver toxicity [36], and Amlodipine too caused serious liver damage [37,38]. This is also evident by our ALP and ALT result of individual Amlodipine, and Levocetirizine treated groups. And it was better regulated by the combination of both the drugs. The reason for this is still unknown; however, it will be interesting to look into the reason for these therapeutic effects. Moreover, it may also clear the answer for the above-mentioned two case studies where such toxicity was reported, and the reason was unknown, our results suggest that stress might have been the reason for this toxicity in the patient.

Furthermore, alteration in these parameters is also correlated to the cardiac remodelling by recent studies. Serum alanine aminotransferase predicts interventricular septum thickness and left ventricular mass in patients with nonalcoholic fatty liver disease [39]. And it was very well regulated by the combination of both drugs. Till date, only liver toxicity with Amlodipine and Levocetirizine is reported in cardiac dysfunction cases. To the best of our knowledge, this is for the first time that under stressful conditions, the combination of Amlodipine and Levocetirizine can reverse the activity of alanine aminotransferase and that may be one of the potential reason to reverse the cardiac remodelling by these drugs in a patient with liver toxicity and cardiac myopathy. The possible reason from the scientific data suggests that under stress, the signals may be passed on to the liver to control the formation and secretion of angiotensinogen, which ultimately converts into angiotensinogen II and other enzymes that may be essential to modulate the activity in the heart to get remodelled [40,41]. This compensatory mechanism may put enough load on the liver to leak these enzymes in the systemic circulation [42]. Nonetheless, the underlying reasons need to be investigated in the futuristic studies to decipher the exact mechanisms involved.

Our study stands by the view that increased serum-uric acid levels are reportedly associated with cardiovascular disease [43]. Calcium channel blockers decrease serum-uric acid levels [44] by the possible pathways such as an

increase in nitrogen monoxide excretion, renal vasodilatory effects and reduction in the production of uric acid precursors such as hypoxanthine in skeletal muscle in patients with hypertension or insulin resistance [45]. Levocetirizine inhibits histamine that up-regulates VCAM-1 expression in fibroblasts, and that is relevant late-phase inflammation [46]. This inhibition of VCAM-1 expression may be the underlining factor for its activity in stress treated rats. The combined effect of Amlodipine and Levocetirizine does not have any significant effect on uric acid reduction in diseased rats; the possible mechanism may be the antagonist effect of Amlodipine and Levocetirizine. Since Amlodipine act as an antioxidant and reduces the ROS levels to show its effect and Levocetirizine inhibit the VCAM-1 expression; they both are antagonizing their effects. Hence there is no net effect on uric acid.

Many reports suggest the relationship between stress and salivary amylase but the research is missing on stress and serum amylase concerning stress and cardiac studies. We studied this parameter as one of the reports that gave the alteration of serum amylase and hypertension [47]. We tried to see the correlation between the stress-induced cardiac remodelling and serum amylase. The results indicate a rise in serum amylase of drug-treated diseased rats and fall in serum amylase when given in combination. Further, it was mentioned in one of the reports that many antihypertensive drugs alter serum amylase [48]. These drugs tend to decrease the amylase levels in serum when the therapy is altered or stopped and can lead to acute pancreatitis [48]. It is difficult to establish the relations between serum amylase and cardiac remodelling under a given set of experimental conditions. However, it can be suggested that this enzyme is one of the cofounding factors for cardiac remodelling in therapy.

5. CONCLUSION

Our study could aid in understanding the synergistic action of both the drugs in the stress-induced remodelled heart. Moreover, the long-term toxicity could also be derogated with this combined therapy on a patient undergoing treatment with Amlodipine. However, the exact mechanism needs further in-depth research at a molecular and cellular level along with the human studies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The experimental procedures were as per the King Abdulaziz University Research Ethics Committee guidelines which are in compliance with the National Commission on the Ethics of Scientific Research at King Abdulaziz City for Science and Technology.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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