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Original Article

POSSIBLE CARDIO-PROTECTIVE EFFECTS OF TELMISARTAN AGAINIST 5-FLUOROURACIL-INDUCED CADIOTOXICITY IN WISTER RATS

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ABSTRACT

Objective: The present study was designed to investigate the protective effects of telmisartan against 5-FU induced cardiotoxicity in Wister rats.

Methods: Thirty-six Wister rats were randomly divided into six groups: I, negative control receiving normal saline (2 ml/kg) orally for 30 successive days; II, positive control receiving normal saline (2ml/kg/day) orally for 25 days, and subsequently received 5-Fluorouracil (5-FU) (20mg in 2ml normal saline per kg body weight) once daily by intraperitoneal injection in association with normal saline for a 5 days; III and IV, receiving telmisartan (5mg and 10mg/kg/day) respectively for 30 successive days; V and VI, receiving telmisartan (5mg and 10mg/kg/day) orally for 25 days, and subsequently received 5-FU (20mg in 2ml normal saline per kg body weight) once daily by intraperitoneal injection in association with normal saline for a 5 days respectively.

Results: Prophylactic treatment of telmisartan significantly attenuates the serum cardiac troponin T, aspartate Aminotransferase (AST) and alanine Aminotransferase (ALT) elevation caused by 5-FU-induced cardiotoxicity.

Conclusion: results of the present finding suggest that telmisartan may be a useful modulator in mitigating 5-FU induced cardiotoxicity.

Keywords: Telmisartan, 5-fluorouracil, Cardioprotective, Cardiac troponin T, AST and ALT.

INTRODUCTION

5-Fluorouracil (5-FU) is still a widely used anticancer drug. Since 1957, it has played an important role in the treatment of colon cancer and is used for patients with breast and other cancers, like those of the head and neck [1]. Due to its structure, 5-FU interferes with nucleoside metabolism and can be incorporated into ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), leading to cytotoxicity and cell death [2, 3]. When combined with radiation therapy, improved local control and survival rates have been reported in a variety of malignancies, compared to radiotherapy alone [4]. However, 5-FU indiscriminate mechanism of action targets not only cancer cells, but all rapidly dividing cells within the body [5], in addition to bone marrow depression, gastrointestinal tract reaction, or even leucopenia and thrombocytopenia [6]. 5-FU has diverse adverse effects such as cardiotoxicity, nephrotoxicity and hepatotoxicity which restrict its wide and extensive clinical usage. It causes marked organ toxicity coupled with increased oxidative stress and apoptosis [7]. The present study was designed to investigate the protective effects of telmisartan against 5-FU induced cardiotoxicity in Wister rats.

Troponin is the contraction-regulating protein complex of striated muscle [8]. Elevated levels of circulating cardiac troponins may have a variety of substrates, such as left ventricular hypertrophy or myocarditis, conditions that may be asymptomatic and are known precursors of heart failure [9, 10]. This has led to a shift in the view of cardiac troponins, from specific identifiers of myocardial infarction to general indicators of myocardial damage [9, 11]. Troponin I and T are specific to the heart, while troponin C can be expressed in skeletal muscle [12, 13].

All components of the renin–angiotensin system (RAS) have been identified in the heart (angiotensinogen, renin, angiotensin converting enzyme (ACE) and angiotensin II (Ang II), receptors) both at messenger ribonucleic acid (mRNA) and at protein level [14, 15] and produced by cardiac fibroblasts (CFs) [16].

In the heart, the local renin–angiotensin system regulates several aspects of both acute and chronic myocardial function [8]. The predominant physiological role of the cardiac renin–angiotensin system appears to be the maintenance of an appropriate cellular milieu, by the balancing of stimuli, induction and inhibition of cell growth and proliferation, as well as mediating adaptive responses to myocardial stress after myocardial stretch (Paul et al. 2006) [17]. Therefore, chronic Ang II type 1 receptors (AT1) receptor stimulation by locally or systemically produced Ang II eventually leads to ventricular remodeling, cardiac hypertrophy (Schluter & Wenzel, 2008) and, ultimately, to the deterioration of systolic and diastolic functions [17].

However, local ANG II levels are increased in pathological conditions, such as myocardial infarction (MI) and in the failing heart [18]. The RAS plays a prominent role in cardiac remodeling during HF development, since increased cardiac ANG II levels lead to cardiac myocyte hypertrophy and myocardial fibrosis [19], proliferation of cardiac fibroblasts [18] and consequently ventricular dysfunction [14]. Sympathetic hyperactivity by activating β-adrenergic receptors (β-AR), stimulates renin and angiotensinogen (Ao) synthesis in fibroblasts and Ao synthesis in cardiac myocytes. ANG II causes changes in gene expression, resulting in the secretion of growth factors and extracellular matrix proteins [18].

A requirement of other factors, such as oxidative stress, inflammation, and aldosterone, has been proposed for ANG II to produce pathological effects in the heart [18, 20] However, these factors may very well be the product of ANG II actions [18]. Through the AT1R, Ang II can also stimulate the release of Interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) and reactive oxygen species (ROS) in macrophages. The signaling pathway involved appears to be the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) /Activator Protein-1 system [21]. IL-1β, TNF-α and IL-6 are the primary regulators of C-reactive protein (CRP) [22]. Several clinical studies have suggested that serum levels of tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), and C-reactive protein (CRP) are elevated in patients with congestive heart failure (CHF) regardless of the etiology of the condition [23].

MATERIALS AND METHODS

Reagents: Standard assay rat's kits ware obtained from SUNLONG BIOTECH CO., LTD., China.

Drugs: 5-fluorouracil obtained from Flakon, Turky and Telmisartan obtained from Boehringer Ingelheim, Germany.

Animals and treatment: Thirty six Wister albino rats weighing 180-250 gm. were brought from the animal house of the College of Pharmacy/University of Baghdad. The animals were maintained on normal conditions of temperature, humidity and light/dark cycle. They were fed standard rodent pellet diet and they have free access to water. The local Research Ethics Committee in College of Pharmacy, University of Baghdad, approved the research protocol. The animals used in this study were classified into six groups six rat of each group as follow: Group I; received single oral daily dose of distilled water (2 ml/kg) for 30 successive days given by oral gavage. Group II; received single oral daily dose of distilled water (2ml/kg body weight/day) orally for 25 days, and subsequently received 5-FU (20mg in 2ml normal saline per kg body weight) once daily by intraperitoneal injection in association with normal saline for a 5 days. Group III; received oral dose of telmisartan (5mg/kg/day) given daily by oral gavage for 30 successive days. Group IV; received oral dose of telmisartan (10mg/kg/day) given daily by oral gavage for 30 successive days. Group V ; received single oral daily dose of telmisartan (5mg/kg/day) orally for 25 days, and subsequently received 5-FU (20mg in 2ml normal saline per kg body weight) once daily by intraperitoneal injection in association with telmisartan for a 5 days. Group VI: received single oral daily dose of telmisartan (10mg/kg/day) orally for 25 days, and subsequently received 5-FU (20mg in 2ml normal saline per kg body weight) once daily by intraperitoneal injection in association with telmisartan for 5 days. All the animals were sacrificed under diethyl ether anesthesia 24 hours later, blood sample were collected from each rat withdrawn from carotid artery at the neck in to labeled centrifuging tubes and allowed to clot for 20 min at room temperature.

Biochemical assessment: The serum was separated by centrifugation at 3000 rpm for 20 min for assessments of biochemical parameters: Rat cardiac troponin T (CTn-T), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT).

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). The Statistical significance of the differences between various groups was determined by student t-test. Differences were considered statically significant for p-value< 0.05.

RESULTS

5-FU (Group II) significantly (P<0.05) increases serum parameters of cardiac troponin T (Fig. 1), AST (Fig. 2), and ALT (Fig. 3) with respect to Group I. Administration of telmisartan in association with 5-FU at a doses of 5mg/kg body weight (Group V) and 10mg/kg body weight (Group VI) significantly (P<0.05) decreases the elevation of cardiac troponin T (Fig. 1) and significantly (P<0.05) decreases the elevation of serum enzymes AST (Fig. 2) and ALT (Fig. 3) with respect to Group II.

Groups III and IV show no significant differences (P<0.05) in cardiac troponin T, AST, and ALT with respect to Group I, while Groups V and VI significantly different (P<0.05) in cardiac troponin T, AST, and ALT with respect to group I, also Group V and VI significantly different (P<0.05) in cardiac troponin T, AST, and ALT with respect to Group III and IV respectively as shown in Fig.1, 2 and 3.

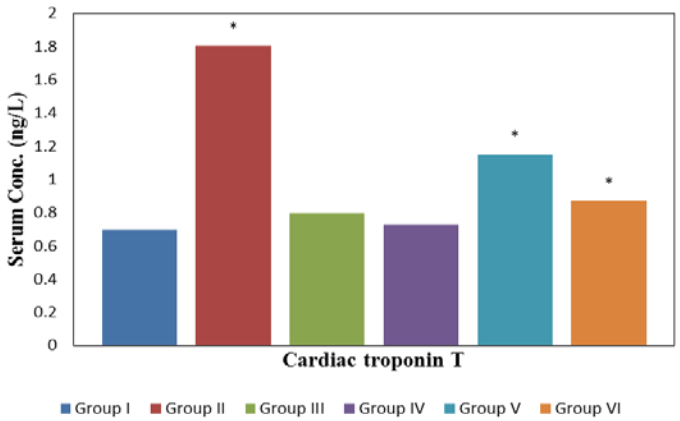

Fig. 1: The effects of telmisartan (5mg and 10mg) on 5-FU induced cardiotoxicity on serum cardiac troponin T.

Data are expressed as Mean±SD, n =6, *p<0.05

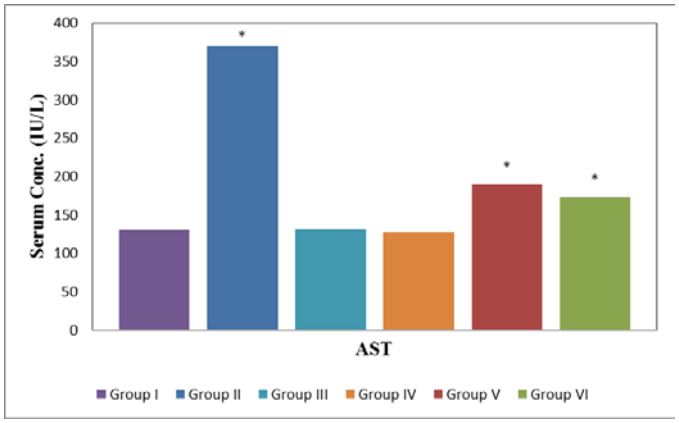

Fig. 2: The effects of telmisartan (5mg and 10mg) on 5-FU induced cardiotoxicity on serum AST.

Data are expressed as Mean±SD, n =6, *p<0.05.

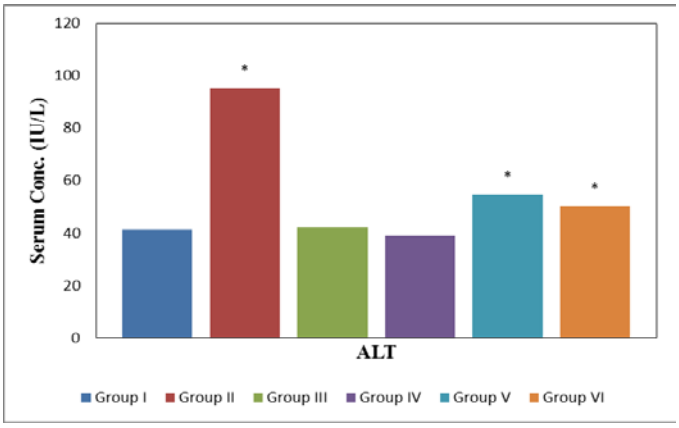

Fig. 1B: The effects of telmisartan (5mg and 10mg) on 5-FU induced cardiotoxicity on serum ALT.

Data are expressed as Mean±SD, n =6, *p<0.05

DISCUSSION

5-fluorouracil (5-FU) is being recognized as a drug with cardiotoxic potential [24]. Pericarditis-like changes after 5-fluorouracil (5-FU) administration have been noted in animal studies. The precise mechanism of 5-FU-induced cardiotoxicity remains undetermined. The most commonly suggested mechanism is coronary vasospasm and myocardial ischaemia [25].

Mechanisms other than vasospasm are likely, at least, in some reported cases of 5-FU cardiotoxicity. Animal studies have shown both pericarditis and myocarditis in rats following 5-FU infusion. Kumar et al postulated that 5-FU-induced endothelial damage leading to extravasation of 5-FU-containing blood into the myocardium could result in an inflammatory reaction. In addition, Matsubara et al administered 5-FU to open chested guinea pigs and showed that Electrocardiography (ECG) changes were not produced by ischaemia, rather a metabolic abnormality due to a direct toxic effect of 5-FU on the myocardium [25]. The present study confirms the cardiotoxicity of 5-FU, as evidenced by the significantly (P<0.05) increases in serum parameters cardiac troponin T, AST, and ALT.

Detection of elevated concentrations of cardiac biomarkers in blood is a sign of cardiac injury which could be due to supply–demand imbalance, toxic effects, or haemodynamic stress [26]. Creatinine kinase (CK), Serum glutamic oxaloacetic transaminase (SGOT) (more recently known as AST), lactate dehydrogenase, myoglobin, and troponins are some of these markers [27]. Because of its high sensitivity and specificity, elevated levels of troponin indicate myocardial damage but not the mechanism of damage [28].

In the last decade, many studies focused on the possibility that inflammation may complicate the clinical course of heart failure (HF) via impairing cardiac contractility, promoting apoptosis and fibrosis and ultimately leading to myocardial remodeling [29, 30]. Ang II can activate phospholipase A2 and the release of arachidonic acid from membrane phospholipids. Arachidonic acid is then converted into thromboxane A2 by the action of cyclooxygenase and into leukotrienes by lipoxygenase [31].

The present study has shown that telmisartan (5mg and 10mg/kg/day) attenuates 5-FU-induced elevation in serum parameters of cardiac troponin T, AST, and ALT in rats. Moreover, the predominant effect of telmisartan reported in the present study may be attributed to other mechanisms specifically utilized by telmisartan, including effective Peroxisome proliferator-activated receptor gamma (PPAR-γ) activation [32]. According to the outcome of the present study, the activity of telmisartan may not be attributed to the Ag II receptor blockade only, and other mechanisms might be involved including PPAR-γ agonist activity. Further studies are highly suggested to compare the activities of different ARB analogues in this model.

CONCLUSIONS

Our results suggest that telmisartan (AT1 receptor antagonist) has a protective effect on 5-FU-induced cardiotoxicity and may be an available agent to protect the myocardium in 5-FU chemotherapy. However, before a conclusive statement can be made on the potential usefulness of AT1 receptor antagonist (telmisartan) as an adjunct to 5-FU therapy, there is a need for further long-term chronic studies with angiotensin receptor blockers.

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