ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Biochemical studies of captopril against 5-Flurouracil induced heart Toxicity in rats

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Manuscript Info

Manuscript History:

Received: 15 February 2015
Final Accepted: 22 March 2015
Published Online: April 2015

Key words:

Captopril,Rats,5-Fluorouracil, HeartToxicity,Cholesterol,Lactate dehydrogenase

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Abstract

Captopril (CAP)is an angiotensin converting enzyme inhibitor and the aim of the present study examined whether, captopril exert beneficial effect on 5-fluorouracil (5-FLU) induced heart toxicity. In the present study twenty four male Sprague-dawley rats were assigned to four equal groups: Group I: rats received normal saline solution (control group); Group II:rats received 5-FLU 20 mg /kg/day, intraperitoneally for 5 days (5-FLU group); Group III: rats received captopril 20 mg /kg/day, orally for 14 days (captopril group); Group IV:rats received 5-FU 20 mg /kg/day, intraperitoneally for 5 days + captopril 20 mg /kg/day, orally for 14 days (5-FLU + captopril group). At the end of experiment animals of all groups were sacrificed, blood and tissue samples from the aorta artery were taken and used for the determination of the investigated biochemical parameters.Injection of 5-FLU causeda significant increase in serum lactate dehydrogenase(LDH) activity and increase in relative heart weight to body weight, serum total cholesterol(TC),triglycerides(TG),low density lipoprotein(LDL), high density lipoprotein(HDL) and malondialdehyde (MDA). In additional, reduced in serum glutathione-s-transferase (GST) was evoked. mineral study showed a significant increase in serum calcium ion (Ca^{++}) and in sodium ion Na^{+} but decrease concentration of K^{+} was noticed compared to control groups.The histopathological study revealed that administration of 5-FLU induced marked alteration in Aortic tissueartery; these included focal inflammatory cells, vacuolar in tunica media, highmagnification and hyalinization.On other hand, administration of CAP and/or 5-FLU, showed improvement in biochemical and histological alterations by decreasing lipid profile, lactate dehydrogenase,lipid oxidation, increasing in GST content and improved the mineral content as well as improving aortic endothelium intima.The present study showed that concomitant captopril use might prevent the side effects of 5- Fluorouracil induced heart toxicity and may be correlated to its antioxidative action of captopril.

1-INTRODUCTION

Many anticancer drugs are cardiotoxicty and5-fluorouracil (5-FLU) one of the mostimportant chemotherapeutic agents used to treat many solid tumors including colorectal cancer (Akihiro, et al.,2013).5-FU is a commonly used chemotherapeutic agent as a part of any cancer treatment protocols, particularly in breast cancer. Itscardio toxicity potential is known but considered uncommon and usually not life threatening(Rajeshwar , 2004).Cytotoxic effects of 5-FU may be exerted by generation of reactive oxygen species (ROS)resulting in apoptosis (programmed cell death)or necrosis (Lamberti et al.,2012).

Metabolism of 5-FLU via a three-step enzymatic process: Capecitabine is first hydrolyzed by carboxylesterase in the liver to the intermediate 5'-deoxy-5-fluorocytidine (5'-DFCR) that is later metabolized to 5'-deoxy-5-fluorouridine (5'- DFUR) by cytidinedeaminase. 5'-DFUR is finallyconverted to 5-FU by thymidine phosphorylase(**Tanakaet al., 2000**). In addition, thymidine phosphorylase is also involvedin the activation of 5-FLU into fluorodeoxyuridine that will further inhibit the DNA synthesis. Concentration of thymidine phosphorylase is 3-10 times higher intumor cells compared to healthy tissue. This can enable selective drug activation of 5-FLU at the tumor site and limit systemic toxicity**(Saif,2007).**
Najam,et al(2014) showedthe comparatively assess direct damages on cardiac tissues and aortaassociated with abnormalities inLDL and cholesterol levelsand cardiac biomarkers induced by two platinum cytotoxiccompounds with and without 5-FLU in rats. Also, Yamamoto,et al. (2007) found that actinomycin D and 5-Fluorouracil induced pica on the first and second day after the drug administration.Al-Shabanah, et al. (1998)studied captoprilamelioratesonmyocardial and hematological toxicities induced by Adriamycin andshowed that lactate dehydrogenase(LDH) and Aspartate transaminase(AST)were improved.

Captopril is an angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension and some types of congestive heart failure. Captopril's main uses are based on its vasodilation and inhibition of some renal function activities. These benefits are most clearly seen in: 1) Hypertension 2) Cardiac conditions such as congestive heart failure and after myocardial infarction 3) Preservation of kidney function in diabetic nephropathy (Habior,1992).Al-Shabanah et al.(1998) suggested that captopril ameliorates doxorubicininduced cardio- and haematotoxicity in normal rats.The protective effect of ACE inhibitors is considered to be mainly the result of reduction in myocardial oxygen demand and an increase in myocardial blood flow by inhibition of angiotensin II formation and bradykinin breakdown (Takeda et al., 1997).

Thereby, this study was designed to investigate the possible ameliorative effect of captopril, on 5-FU-induced cardiac injury in rats.

2-MATERIALS AND METHODS

Twenty four Sprague –Dawely male rats weighing 150± g were obtained from the breading unit of Egyptian organization for biological and vaccine production,A.R.E .,the animals were housed under standard laboratory conditions.They were kept on vegetables and water ad libitum for one week prior to the experiment.

2.1Chemicals

Captopril used in this experiment were obtainedfrom (sigma-Aldrich chemical co., st.Louis, Mo, USA,was dissolved in normal saline.Captoprilwas administered by oral gavage at a dose of(20mg/kg) according to Shin et al. (2009).
5-FU was given intraperitoneally at a dose of 20 mg/kg that was guided by previous studies (Nayciet al., 2003&El-Sayyad et al., 2009)

2.3. Experimental groupsand protocols

Rats were divided into four groups (6 rats each) and treated as follows:
1-**Control group:**These animals received (2/kg b.w/day).ml of normal saline by oral gavage for 14 days.
2-**5-**FLU **group**: The animals first received normal saline (2 ml/kg b.w./day) orally for 9 days, and subsequently received 5-FLU (20 mg in 2ml normal saline per kg b.w.) once daily by intraperitoneal injection(i.p.) for additional 5 days.
3-**CAP group**:Rats received orally (20mg/kg) captopril for 9 days and subsequently received normal saline once dailyby i.p injection in association with captopril for additional 5 days.

4- **5-FLU + CAP group: Rats** . received captopril(20mg/kg) daily for 14 days oral and in the 9th day injected rats i.p by 5-fluorouracil for 5days (20mg/kg)

At the end of experiment the animals were sacrificed and blood was collected by carotid bleeding in centrifuge tubes and then centrifuged at 3000 rpm for 15 minutes to separated serum and stored at -20C for biochemical analysis. Aorta arterieswere quickly harvested.

2.4.Biochemical analysis:

Total serum cholesterol was measured by kits of Schettler and Nissel(1975).Determination of HDL-cholesterol by method of Lopez et al(1977).Triglycerides was measured according toFassati(1982).
Serum lactate dehydrogenase (LDH)was measured by kinetic method according to Young(1990).
Malondialdehyde(MDA) was determined using the method of Ohkawa et al(1979). Serum glutathione-s-transferase(GST) activity was assayed spectrophotomertrically by the method of Habiget al.(1974).Serum minerals contents of sodium andpotassium were assessed using atomic absorption spectrophotometery(Zettner andSeligson,1964) and calcium(Ca^{++}) ion by colorimetric method by Gindler and King(1972) .

2.5.Histopathological studies:

Autopsy samples were taken blood vessels (Aorta arteries) in different groups of rats and fixed in 10% formal saline for twenty four hours.Washing was done in tap water then serial dilutions of alcohol(methyl, ethyl and absolute ethyl) were used for dehydration. Specimens werecleared inxylene embedded in paraffin at 56 degree in hot air oven for twenty four hours.

Paraffin bees wax tissue blocks were prepared for sectioning at 4 microns thickness by slidge microtome.The obtained tissue sections were collected on glass slides, deparaffinized and stained by hematoxylin and eosin stain for histopathologial examination through the electric light microscope(Banchroftet al .,1996)

2.6.Statistical analysis:

All data were analyzed using the SPSS for windows (version 12.0). Analysis of variance (one- way ANOVA) was performed to test for any significant differences among groups and independent sample t-test was used to calculate statistical significant between the control group and each treated group .The level of significancewas set as $P< 0.05$ for all statistical tests(Telloet al.,2003)

3. **Results**

3.1.Biochemical results:

The results in Table (1)showed that captopril (CAP) induce significant decrease in the serum level of lipid profile in comparison to rats treated with 5-Fluorouracil (5-Flu). Also, after receiving(CAP plus 5-FLU) there were a highly significant decrease in total cholesterol, low density lipoprotein , triglycerides and high density lipoprotein levels, compared to control.

Table (2) showed the effect of CAP on MDA, GST ,LDH , heart weight and body weight on rats treated with 5-Flu. The data concerned with changes of MAD, LDH,body and heart weight where, a highly significant increase were recorded in rats treated with (5-FLU), while, GSTshowed a highly significant decrease, compared to control. After treatment with CAP plus 5- Flu a highly improvement was achieved for MDA ,GST, body and heart weights as well as LDH levels,compared to control.

The data in Table (3)showed a highly significant increase in serum content of Na^{+}andCa^{++}in rats treated with 5-Flu ,compared to control. While, decreasing of serum K^{+} contentwas recorded.The treatment with CAP plus 5-Flu induced significant reduction in serumNa^{+}andCa^{++} ion sand significant increase in the level of K^{+} content, compared to control

3. 2.Histopathological results:
Control group

Fig.(1)Photomicrograph of aorta vessel of normal control rats showing normal histological structure of intima ,media and adventitia
(H&E x160)

Examination of H&E stained blood vessels (Aorta) sections obtained from control rats Fig(1) revealed a normal wall of aorta being formed of three coats , an inner the tunica intima consists of endothelium squamous cells followed by wavy lamina of elastic connective tissue. Tunica media consists of circular unstriatedmuscle ,fibres held together by elastic and collagenous connective tissue fibres, also tunica adventitia consists of a reolar connective tissue.

There was no histopathological alteration observed and the normal histological structure of the intima ,media and adventitia were recorded in Fig(1)

5-FLU-treated group

Figs. (2,3) Photomicrograph of aorta vessel of treated rats with 5-FLU, showing focal inflammatory cells, vacuolar in tunica media(m) also, show high magnification tunica media hyalinization(H) in the media(m)
(H&E x160)

Also, Histological evaluation of 5- Flu, treated group in Figs(2,3) showed focal inflammatory cells, vacuolar in tunica media(m), also show high magnification, hyalinization (H) in the media(m)

CAP plus 5-FLU -treated group

Figs.(4,5) Photomicrograph of aorta vessel of treated rats with
(5-FLU)-induced histopathological changes but protection of rats
with(CAP) nearly normalized showing improvement histological
Structure of the media of aorta vessels also,showing the magnification to identify the normal histopathological
Structure of media (m)
(H&E x160)

In this group protection of rats with CAP nearly normalized after the 5-Flu- induced histopathological changes.Blood vessels of rats showing improvement histological structure of the media and showing the magnification (Figs 4,5) to identify the normal histological structure of the media (m)

Table (1): The effect of CAP on 5-FLU Induced changes in serum lipid profile of rats TC, HDL, LDL and TG of rats.

Groups	TC mg/dl	HDL mg/dl	LDL mg/dl	TG mg/dl
Control	78.75^{c}±2.47	30.35^{c}±0.33	11.14^{c}±0.031	130.16^{c}±0.31
5-Flu	121.50^{a}±4.52	46.44^{a}±0.84	28.00^{a}+0.62	193.16^{a}±2.28
Cap	77.73^{c}±2.52	30.0^{c}±0.32	10.73^{c}±0.10	130.33^{c}±0.33
5-Flu+Cap	92.98^{b}±1.43	39.46^{b}±0.26	21.41^{b}±0.37	149.50^{b}±1.64

Mean ± S.E (n= 6 in each gram)

Table (2): The effect of cap on MDA, GST, B.wt, H.wt and LDH contents of rattreated with 5-Flu relative heast.

Groups	MDA (nmol/L)	GST (nmol/L)	Body weight (g)	Heart weight (g)	LDH (u/L)
Control	105^{b}±0.99	436.46^{a}±8.31	150.83^{b}+2.0	0.281^{c}±0.02	445.33^{c} ±2.24
5-Flu	171.33^{a}±14.29	265.20^{d}±10.87	164.16^{a}±4.36	0.431^{b}±0.036	576.66^{a}±5.57
Cap	111.50^{b}±1.11	415.59^{b}±2.42	166.66^{a}±1.05	0.571^{a}±0.016	441.33^{c}±0.33
5-Flu+Cap	120.83^{b}±2.63	385.81^{c}±0.004	152.50^{b}±1.70	0.401^{b}±0.040	512.0^{b}±0.577

Mean ± S.E (n= 6 in each gram)

Table (3): The effect of cap Na+, K+ and Ca++ in serum content of rats treated with 5-Flu.

Groups	Na+ (gm/L)	K+ (gm/L)	Ca++ (gm/L)
Control	128.83^{c}+1.24	5.61^{a}+0.13	6.95^{bc}+0.46
5-Flu	161.33^{a}+1.87	2.73^{c}+0.20	9.90^{b}+0.08
Cap	131.0^{c}+1.82	5.0^{b}+0.081	7.43^{b}+0.18
5-Flu+Cap	135.83^{b}+0.40	4.91^{b}+0.04	6.86^{c}+0.23

Mean ± S.E (n= 6 in each gram)

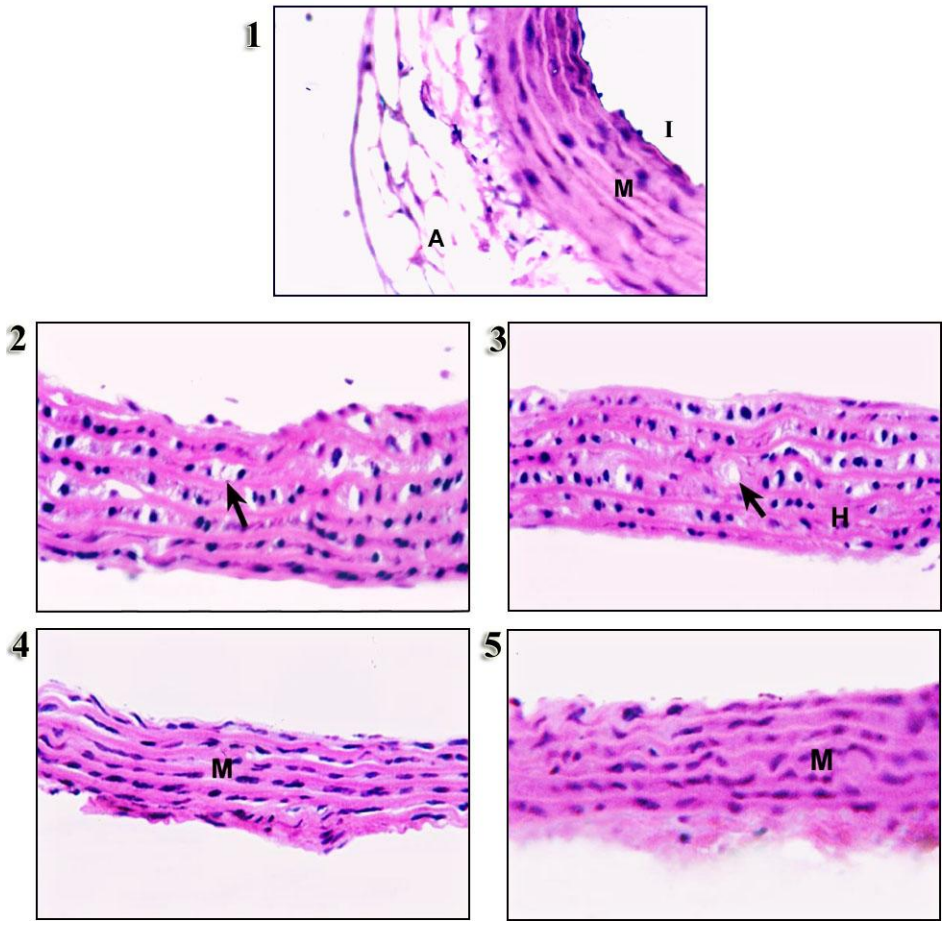

Fig. (**1**) Photomicrograph of aorta vessel of normal control rats showing normal histological structure of intima (A), media (M) and adventitia (I)
(H&E x160)

Figs. (**2, 3**) Photomicrograph of aorta vessel of treated rats with 5-FLU, showing focal inflammatory cells, vacuolar in tunica media (M) also, show high magnification tunica media hyalinization (H) in the media (M)
(H&E x160)

Figs. (**4, 5**) Photomicrograph of aorta vessel of treated rats with 5-FLU, -induced histopathological changes but protection of rats with CAP nearly normalized showing improvement histological structure of the media of aorta vessels also,showing the magnification to identify the normal histopathological Structure of media (M)
(H&E x160)

4.Discussion

Data of the present study showed that 5-Flu administration produced significant increase in total cholesterol,Triglycerides, low density lipoprotein and lactate dehydrogenase while, high density lipoprotein was decrease ,Also, increase in body and,heart weight ,Ca^{++} ion,Na^{+} ion and decrease in k^{+} ion these results agreement with(Patel etal., 2010) and(Bilginoglu etal., 2014) which ,studied of cardioprotective of melatonin and show that Lipids play an important role in cardiovascular diseases due to the structure and stability of the cellular membranes The results of their studies showed a significant elevation in the level of triglycerides in the serum of the adriamycin-treated group.
There were also some increases in LDL fraction , which implies that adriamycin (is one of the most widely used anti-cancer drugs) as 5-FLU toxicity is dependent upon the cumulative dose. Described

By(Iliskovic et al.,1997) . In contrast, we showed that there was a decrease in HDL-cholesterol level in the adriamycin administration group. With these results in the lipid profile, the lipid fraction may be diluted and delay their lipolysis and utilization. The pre-cotreatment with melatonin successfully restored the elevated triglycerides, LDL-cholesterol and

also, increase in LDH in 5 FLU- treated rats agrement with, (Bilginoglu etal.,2014) The degree of adriamycin-induced cardiotoxicity was assessed chemically by determining the level LDH, In comparison to the control group, the adriamycin-treated group showed significant elevation in the levels of cardiac marker enzymes in the serum. reports This effect may be due to indication of adriamycin-induced necrotic damage of the myocardium and leakiness of the plasma membrane,and increase lipids in serum due to increase body and heart weights

Lemaire et al .(1992 and1994) ,show that the cardioyoxicity of 5- FLU might have at least two origins .the first in the presence of fluorinated impurities in commercial solution of 5-FLU derived from the degradation of FLU in the basic medium required for its solubilization, which are metabolized into FHPA and FAC . The second is the metabolism of FLU itself into these two cardiotoxic compound .(Lemaire et al., 1992) Reported that the original aim of his study was to relate the cardiotoxicity of FLU to metabolism of the drug in the heart .indead Japanese workers had reported that ECG changes elicited by i.v. administration of FLU to the guinea pig were associated with intracellular depletion of high energy phosphate compounds and asubstantial elevation of intany o-cardial citrate level

Via protein kinase also (Tsavaris et al., 2002) The present study supports the toxic effect of 5-FLU on myocardium, which is largely schedule- dependent considerable vigilance is required when using this drug and its toxic effect on the coronary endothelium and myocardium merit further investigation(Kuropkat et al., 1999) said that endomyocardial biopsy showed proliferation of the sarcoplasmic eticulum with marked vascuolization , similar to that found with doxorubicincardiotoxicity. Suggested mechanism is that 5-FU may cause metabolic changes producing hypoxia within myocardial cells

Other histomorphological and biochemical studies indicate amore direct drug 5-FLU mediated cytotoxic action and has direct endothelial toxicity resulting in thrombogenic effect and release of vasoactive substances(Kloner et al., 1991)
(Alter et al., 2006) report that, mechanism of cardiotoxicity ranging from direct toxic effect on vascular endothelium involving endothelial. No synthase leading to coronary spasms and endothelium independent vasoconstriction

It has been suggested that raltitrexed might be an alternative for patients with the cardiotoxic advanced colorectal cancer and 5-FLU associated cordiotoxicity ,effect of 5-FLU itself may be responsible for 5-FLU cardiotoxicity .Inhibition of DNA synthesis by 5-FLU incorporated into myocardial cells was suggested to be the first step of cardiotoxicity (Kohne et al., 1998)

Like 5-FLU, raltitrexed exerts similar effects on DNA synthesis.This DNA –directed antimetabolite mechanism is there for avery unlikely cause of 5-FLU cardiotoxity. As the recurrence rate of

cardiotoxicity after exposure to 5-FLU is thought to be 90%(Robben et al., 1993) cardio toxic side effects after atotal of seven exposures to raltitrexed would have been expected, assuming that the direct cytotoxic effect on DNA synthesis is responsible for cardiotoxicity

(Ensley et a.l., 1989 & Sihgh et al., 2004) suggest that ,coronary artery spam has been documented angiographically following intravenous 5-FLU administration and prophylaxis with calcium channel antagonists has been successfully employed in preventing recurrence
Luwaert, et al., 1991) A nalternative.

(Mohamed et al. , 2009 and Alter et al., 2005)Ischema could be due to adirect toxic effect on the vascular endothelium involving No synthase which leads to coronary vasospasms. The other mechanisms of vasospasm endothelial vasoconstriction is via protein kinase

(Spasojevic et al., 2008) have performed an ex vivo and in vivo study effects of cisplatin and 5-FLU on erythrocytes using avariety biophysical techniques .Their research showed 5-FLU provoked a pronounced decrease of O2 level in blood and affected the metabolism of phosphate compound while cisplatin had no such effects. They suggested decrease oxygen transfer capacity of erythrocytes as cause of 5-FLU related ischemia (Papadopoulos, and Wilson 2008)Toxicity with drug 5-FLU ranged awide spectrum with mechanisms from coronary vasospasms and(Hala, 2012) reported tha light microscopic observations revealed that administration of 5-FLU caused signs of cardiotoxicity,which are represented by focal atrophy and coagulative necrosis as well as cytolysis of myocytes,study 5-FLU was found to cause significant kindy injury manifested biochemically increase , malondialdehyde and potassium and decrease in sodium and glutathione these result are consistent with previous studies by other investigators(Ga et al., 2006 and Nora, 2012) that 5-FLU induced nephrotoxicity in normal rats.

On the other hand the present results illustrated that captopril administration had an angiotensin converting enzyme inhibitor and was widely used in the treatment of cardiovascular disease(Yun et al.,2005).Also, they found that captopril can restore endothelium- dependent relaxation of rat aortic rings after exposure to homocysteine(Fu, et al.,2003)

Captopril presented the protective effects against endothelium damge induced by hyper cholesterolemia and oxygen free radicals(Hernandez et al.,1998 & Ota et al., 1997).

In addition, Captopril also concomitantly decreased the serum levels of MDA derived from lipid peroxidation and increase GST activity in rats agree with (Napoli et al. ,2004) reported that beneficial effect of Captopril on homocycteine-induced endothelial dysfunction is related to the reduction of endogenous asymmetric dimethylarginine(ADMA),also may be to its antioxidant activity recently, reported that another new sulfhydryl angiotensin converting enzyme inhibitor zofenopril reduces oxidative stress.

Also,(Martinez and Villalobos,2003) found early and chronic therapy with low doses of Captopril prevented heart failure(CHF) establishment probably by limiting expansion of infacted
area after coronary occlusion and suggested AT1 receptor pathway involvement in this pathology.

Deng et al,(2001) reported that captopril attenuates oxidative stress ROS. No interaction and no production by decreasing angiotensin II that regulates nicotinamide-adenine- dinucleotide phosphate oxidase which is thought to be amajor source of ROS(Jones et al,1996).

Furthermore, Yang et al,(2001) there is now mounting evidence that ACELS exert at least some of their beneficial effects by inhibition of degradation of the endogenous vasodilator bradykinn as well . The beneficial role of captopril in treatment of congestive heart failure, an effect that may be related to its free radicals scavenging and antioxidant effects which are sulfhydryl dependent (El Sayedetal.(2008)

Mahmoud, et al .,1999 and Aruoma et al.,1991 reported to Captopril has been reported to react rapidly with hydroxyl radicals and hypochlorous acid at micromolar concentration.

The increase in heart weight and body weight indicates reactive hyper trophy(Kalkman,et al.,1997) and the effect which was prevented by captopril may be related to loss of retained body fluid due to reduced angiotenin II and aldosterone levels.
(Van krimpen,) et al,1991 reported that any effect of captopril treatment on either heart weight or collagen content and associated increase DNA synthesis.

The decreasing of lactate dehydrogenase in our study agree with(Kalkman, 1996b) due to decrease oxygen diffusion distance and therefore contribute to better preservation of an aerobic metabolism

Sodium ion decrease according to Campbell etal,1982 suggested that the converting enzyme inhibitor captopril, produced an initial blood pressure reduction in patients with essential hypertension. The result suggest that hypotensive effect of captoppril is mediated through angiotension converting enzyme inhibition possible that the early addition of of a diuretic may allow control to be achieved at low dose of captopril with reduction in risk of toxic side effects.

Formation from calcium ionosphere- stimulated neutrophil,therefore, it is possible that captopril may protect the renal tissues against 5-fu induced renal toxicity by indirectly inhibiting the generation of superoxide anion via inhibition of leukotrieneB4 formation(Nora, 2012)
myocardial depression has been explained by inhibition of mitochondrial DNA synthesis due to 5-FLU (Akhtar et al.,1993). Also,(Michael et al.,2013) report that, 5-FLU interferes with DNA synthesis in cancer cells leading to cell death

With supported that improve effect of captopril on vessel (aorta)structure by the lack of interference with vascular growth by captopril(cap) and CAP +5-Flu group in our study these agreement with (Le Noble et al.,199,3munzenmaier and Greene, 1996) may be interpreted as paradoxical finding because angiotensin II is recognized angiogenic factor ,Another potential mechanism for angiotensin converting enzyme angiotensin AT2 receptor-mediated inhibition of endothelial cell proliferation and could be average vessel diameter was increased after captopril (Stoll et al. ,1995) Light microscopic of cardiac muscle observations revealed that administration of 5-fu caused variable signs of cardiotoxicity which are represented by(Hala, 2012) found that focal atrophy vacuolar degeneration, coagulative necrosis as well as cytolysis
Aprobable reason has been proposed,It explains the endothelial damge leading to extravasation of the drug containing blood into myocardium resulting in myofibril necrosis and inflammatory reaction,(Kumar et al.,1995) and (Alter et al.,2006) ,suggests . The mechanism of 5-FLU associated cardio toxicity is controversial but the prevalent hypothesis show ischemia to the myocardium. Ischemia could be due to a directtoxic effect of vascular endothelium involving no synthase, which lead to coronary vasospasms.The other mechanism of vasospasm endothelial is via protein kinase(RKC) –vasocontriction(Alter et al., 2006).In the present study treatment with captopril could obviously miligate the marked cardiotoxicty induced by 5-FU, resulting in morphology to the control group.This observation is similar to results of(Okada et al .,2008) showed that captopril inhibits monocrotaline induced of hypertrophy and fibrosis in the right ventricle of rats .Moreover

,(Sacco et al .,2009) demonstrated that inhibition of cardiac ACE by zofenopril and additional cardio protective mechanisms may havearole in its ability to prevent myocardial damages in the rat subjected to chronic anthracyctinetreatment.Captopril has suphydryl group and can be converted inodisulphides through the interaction with free radicals instead of cellular sulphydryl. Containing proteins and enzymes(Pi and Chen , 1989) .Consistent with the reports ,the presents results showed that captopril inhibits monocrotaline induced right ventricular hypertrophy as well as fibrosis(Okada et al., 2008) and left ventricle interventricular septum weight hail lengh ration was decreased by captopril in our experment

With supportedthat improve effect of captopril on vessel (Aorta) structure by the lack of interference with vascular growth by CAP and CAP plus 5-Flu groups in our study ,these agreement with(Le Noble et al., 1993;Munzenmaier and Greene, 1996) May be interpreted as paradoxical finding because angiotensin II is recongnizedangiogenic factor. Another potential mechanism for angiotensin converting enzyme inhibitor-induced stimulation of vascular growth may be reduction of angiotensin AT2 receptor – mediated inhibition of endothelial cell proliferation and could be average vessel diameter was increased after captopril (Stoll et al.,1995)

In conclusion,the current study suggests that captopril may has Therapeutic value in lowering cardio toxicity which, induced by 5-f luorouracil due to reducing serum lipid profile

REFERENCES

Akhtar,S.S., Salim,K.P., Bano, Z.A.,1993Symptomatic cardiotoxity
With high- doses 5-fluorouracil infusion: aprospective
Study.
Oncology, 50: 441-444.

Akihiro,,E .,Yasuyuki,Y. M .D., Ryuma ,N.M.D., Nobuyuki,T.M.D .,
Kazuaki,,T.M.D.,2013
Capecitabine induces both cardiomyopathy and multifocal
Cerebral leukoencephalopathy .
Int .Heart,54:417-420.

Al-Shabanah, O., Mansour, M., Al-Kashef, H., ALBekairi ,A., 1998: Captopril ameliorates myocardial and .
hematological toxicities induced by adriamycin. Biochem Mol Biol Int.; **45(2):** 419-27

Alter ,P. M.,Herzum,M.,Soufi,,J.R,. Schaefer and Maisch,B.,2006.
Cardiotoxicity of 5-fluorouracil cardiovasc. Haematol.Agent
Agents Med. Chem.,4(1):1-5.

Shahrokni,A., Mohammad R .R., Harold,,L., Muhammad W. S,.2009
Cardiotoxicity of 5-Fluorouracil and Capecitabine in a PancreaticCancer Patient with a
NovelMutationin the Dihydropyrimidine Dehydrogenase Gene

JOP. J Pancreas (Online) Mar 9; 10(2):215-220.

Aruma,,o .; Akanuma, D. ;Cecchini,R.;Halliwell,B.,1991
Evaluation of the ability of the angiotensin-converting
enzyme inhibitor captopril to scavenge reactive oxygen
species.Chem-Bio(interact),77:303-314.

Banchroft, J.D. ; Stevens,A., Turner,D.R,1996. Theory and practice of histological Techniques Fourth
Ed.Churchil livingstone ,New York,London,San Francisco,Tokyo.

Bilginoğlu, A. M.D., Aydın, D. M.D. , Özsoy,S. M. , Aygün, H.M.D.* (2014) Protective effect of
melatonin on adriamycin-induced cardiotoxicity in rats **Türk Kardiyol Dern Arş - Arch Turk Soc Cardiol ;42(3):265-273**

Bozdag,A.D.,Peker,H.,Derici,C.Gurko, k. , Ozgonul,M.,2001
The effect of preoperative 5-fluorouracil on colonic healing
: an experimental study.Hepatogastroenterology,
48(42):1631-1634.

Bultzingslowen,,I ., Jontell, M.,1999.
Macrophages,dendritic cells and T lymphocytes in rat buccal mucosa and dental pulp following.
5-Fluorouracil treatment
Eur J Oral Sci Jun;107(3):197-201

Cody, R .J. ,1986.Conceptual and therapeutic approaches to inhibition .
of the rennin –angiotensin system in chronic heart failure J Cardiovasc pharmacol,8:58-

Colak,T.;Dag A. ;Turkmenoglu,O. ;Polat, A. ;Comelekoglu, U.Bagdatoglu ,O.;POLAT,G.;Akca,T.;Sucullu,I.; Aydin, S. , 2007 .The effect of octreotide on healing of injured Colonic anastomosis with immediate Postoperative intra peritoneal administration of 5-Fluorouracil. Dis Colon Rectum May;50(5)660-9 .

Deng,G.;Vaziri ,N.D.;Jabbari,B.; Ni,Z., Yan,x.x.,2001 . Increase Tyrosine nitration of the brain in chronic renal Insufficiency :reversal by antioxidant therapy and

Angiotensin –converting enzyme inhibition. J Am . Soc.Nephrol., 12:1892-1899.

El-Hoseany, M.N.,2012 .
.Protective effect of captopril against 5- Fluorouracil-induced hepato and nephrotoxicity

In male rats

Journal of American science,8(2):680-685.

El-Sayed H.I.,Ismail ,M.F.,Shalaby,F.M.,Abou –El-Magd,R.F.,Gaur,R.L.,Fernando,A.,Ra,jM.H., Ouhtit,A.,2009.Histopathological effects of Cisplatin,doxorubicin and 5-fluorouracil(5-FLU) On the liver of male albino rats.Int.j.Biol.Sci. 5(5):466-473.

El-Sayed, M.S.; Mohamed,F.Aand Sabry,M.A.,2008. protective effect on Captopril against cisplatin- induced Nephrotoxicity in rats.J.Pharm.Sci.21,3pp.255-261.

Ensley,J..F.patel,,R.,Kloner,J.A.,Kish,J.Wynne , Al-Sarraf,M.,1989. The clinical syndrome of 5-fluorouracil(5-FLU) Cardiotoxicity. Invest .New Drugs,7(1):101-109.

Fassati, P. and Prencipe ,L.,1982 Enzymatic colorimetric method of serum triglycerides Clin.Chem., 28 .2077.

Francis , G.S.,1985. Neurohumoral mechanisms involved in congestive heart failure. Am .J cardial, 55: 15A -21A.

Fu ,Y.F.,Xiong ,Y FU., SH., 2003 Captopril restores the endothelium dependent relaxation Of rat aortic rings after exposure to homocyctein J .Cardiovasc .Pharmacol .42 ,566-572.

Gao L, M.A. R., Zhou, J. , Cheng, S., 2006: Changes of serum erythropoietin during Cisplatin- or 5-Fluorouracil-induced anemia in rats. Toxicol Mech Methods. 16(9):501-506.

Gindler,,M., King, J.D.,1972.

Colorimetric method of serum calcium content
Am. J .Clin .Path 58, 376.

Habig ,W. , Pabst, M . Jakoby , W.,1974
Biodiagnostic glutathione ,S-Transferase Assay KIT
Measures total G S T activity
J . Biol .Chem 249 , 7130 - 7139.

J . Biol .Chem 249 , 7130 - 7139.

Hala, F . A,. Ameliorative effect of captopril against

5-Fluorouracil –induced cardiotoxity in rats :A study with
Light and electron microscopes.
Journal of applied sciences research8(1):1-10

Hemandez ,A ., Barberi,L., Ballerio ,R .,Testini A.. , Ferioli ,R ., Bolta ,M .
Natali , M ., Folco ,G.,Catapano, A.L.,1998.
Delapril shows the progression of atherosclerosis and
Maintains endothelial function in cholesterol fed rabbit
Atherosclerosis 137 , 71-76

Humason ,G .L.,1979 .Animal tissue , Fourth Edition .san Fransisco. W .
H. Freem and company.

Ibrahim, M.A., Ashour ,O.M., Ibrahim, Y.F., El-Bitar, H.I., Gomaa, W., Abdel-Rahim, S.R.,2009 Iliskovic N,
Angiotensinconverting enzyme inhibition and angiotensin AT(1)-receptor antagonism equally improve
doxorubicin-induced cardiotoxicity and nephrotoxicity. Pharmacol Res., 60:378-381

Singal ,P.K.,1997. Lipid lowering: an important factor
in preventing adriamycin-induced heart failure. Am J Pathol
;150:727-34.

Jones .S.A., Donnell, O.V.B., Wood , J. D., Broughton ,J.P. ,Hughes E.J
Jones ,O.T.,1996
Expression of phagocyte NAD PH oxidase components
in human endothelial cells
Am .J Physiol. 271:H 1626 – H 1634.

Kalkman, E.A. ,Saxena, P.R. ,Schoemaker, R.G. ,1996 b.Sensitivity to
ischema of chronically infracted rat hearts .Effects of
long- term captopril treatment.
Eur .J.Pharmacol, 298,121-128.

Kuropkat,C.K.,Griem,J.,Clark,E.R,Rodriguez,J.,Hutchinson
andTaylor,S.G.,1999.Severe cardiotoxicity during
5- fluorouracil chemotherapy :case and literature
Report.Am.J.Clin.Oncol.,22(5):466-470.

Lamberti, M.L, Porto S., Marra, M.I.,2012 . 5-Fluorouracil induced apoptosis in rat cardiocytes through
Oxidative stress. J ExperClin Cancer Res. ; 31: 60. doi:10.1186/1756-9966-31-60

Lemaire,,L..,Malet-Martino, M.C.,De Forni,M.,Martino, R. ,

Lasserre,,B.,1992. Cardiotoxicity of commercial
5- fluorouracil vials stems from the alkaline

Hydrolysis of this drug Br.J.Cancer,66(1):119-127.

Le Noble ,F.A.,Schreus,N.H. ,Straaten ,V.H.W,Slaaf, D.W.,Smits, J.F,R ogg, H., Boudier,S.H.A. ,1993. Evidence for a novel angiotensin II receptor involved In angiogenesis in chick embryo chorioallantoic Membrane. Am.J.Physiol .264 ,R 460-R 465.

Lopez ,V.M.Fl., 1977. Enzymatic colorimetric method for measuring serum HDL cholesterol. Clin .Chem .23,882.

Martinez ,L.A. , Molina ,V., 2003. Early and chronic captopril or losartan therapy reduces Infact size and avoids congestive heart failure after myocardial infarction in rats. Archives of medical research 34 : 357 -361.

Mahmoud ,A.M. , Hassan,A.K.. , Othman ,A.S.H.,1999 . Effect of captopril on doxorubicin -induced nephrotoxicity in normal rats Pharmacological Research, 39,3:233-237.

Michael, F. S ., Jiwon, K.. , Andrew, E. F ., Alexander, G. T ., (2012).

5-fluorouracil induced cardiotoxicity:

Review of the literature

Cardiology Journal, 19, No. 5, pp. 453–458.

Michael,G.,Fradley M.D., Conor, D.,Barrett ,M.D.,Sanjeev,A ., Francis, M.D.,2013Ventricular fibrillation cardiac arrest due to 5-fluorouracil cardiotoxicity (2013). Tex Heart Inst.J.,40(4):472-478.

Mohamed, H., Abou El Fadl, M .D.,2009 **5-Fluorouracil–Induced Cardiotoxicity During Chemotherapy for Adenocarcinoma of the Small Bowel** International Society of Gastrointestinal Oncology Volume 3 • Issue 4:167- 170.

Munzenmaier,,D.H.,Greene,A.S., 1996 Opposing actions of angiotensin II on microvasculare Growth and arterial blood pressure L.H.Hypertension .27 , 760-765.

Najam, R., Bano N,Mirza T., Hassan S.,2014 .Adverse effect on Cardiovascular status and lipid levels of albino wistar Rats treated with cisplatin and oxaliplatin in Combination with 5Fluorouracil. Pak J Pharm sci,27(5):1409-1418.

Napoli ,C. ,Sica ,V., de Nigris ,F. ,Pignalosa ,O., Condorelli ,M ., Ignarro ,

L.J .,Liguori,A .,2004
Sulfhydryl angiotensin-converting enzyme
inhibition induces sustained reduction of systemic
oxidative stress and improves the nitric oxide
pathway in patients with essential hypertension

Am Heart J. 148 , e5

Nora,,E.A.,2012. Protective Effect of Captopril against 5- Fluorouracil-Induced Hepato and Nephrotoxicity in Male Albino Rats.

Journal of American Science, 2012;8(2):680 – 684.

Ohkawa, H. ,Ohishi ,W.and Yagi ,K.,1979.
Colorimetric method for determination MDA,
Anal .Biochem ,95 ,351

Okada,M..,Kikuzuki,R.,Harda,T.,Horni,Y.,Yamawaki,H.,andHara,Y., 2008
Captopril Attenuates Matrix Metalloproteinase-2 and-9 in Monocrotaline-Induced Right Ventricular Hypertrophy in Rats
J Pharmacol Sci 108, 487-494
Ota ,Y.,Kugiyama ,K.,Sugiyama ,S ., Ohgushi, M .,Matsumura ,T. ,Doi,
H.,Ogata,N.,Oke ,H., Yasue,H .,1997.
Impairment of endothelium dependent relaxation of
Rabbit aortas by cigarette smoke extract-role of free
Radicals attenuation by captopril
Atherosclerosis 131, 195 -202.

.
Patel V, Upaganlawar A, Zalawadia R, Balaraman R.,2010 Cardioprotective
effect of melatonin against isoproterenol induced
myocardial infarction in rats: A biochemical, electrocardiographic
and histoarchitectural evaluation. Eur J Pharmacol .644: 160-8

Rajeshwar,S ., Sagar, T.G ., Ramanan, S.G.,2004

fluorouracil cardiotoxicity revisited

Indian J OF Medical & PaediatiIc Oncology

Vol. 25 No.4, 35-38

Robben, N.C., Pippas, A.W., Moore, J.O., The syndrome of 5-

fluorouracil cardiotoxicity. An elusive cardiomyopathy.
Cancer 1993;71:493–509
Sacco,G .,MarioB.,Lopez,G.,Evangelista,S.,Manzini,S.,Maggi,C.A.,
2009.ACE inhibition and protection from doxorubicin
-induced cardiotoxicity in the rat .
Vascul. Pharmacol.,50(5-6):166-170.

Schettler, G ., Nussel ,E.,1975.
Determination of serum total cholesterol by enzymatic
Colorimetric test .
Arb .Med . Soz - Med .Prar .Med 10 , 25.

Shin, C. Y., Choi, W. S. Yi, L. Nan, M.H .,
Myung, C.S. ,2009 :Synergistic decrease in blood
pressure by captopril combined with Losartan
spotaneous hypertensive rats. Arch. Pharma. Res.,
32 (6) 955-962.

Singh,R.,Sagar,T.G . Ramanan,S.G.,2004 .
5-fluorouracil cardiotoxicity. revisited .Case report-II.Indian J Med
Paediatr. Oncol.,25(4):35-38.

Spasojević ,I., Jelić, S., Zakrzewska, J. , Bacić, G. ,2005.3IP NMR
treate spectroscopy And polarographic combined study of erythrocytes
with5-fluorouracil: cardiotoxicity –related changes in ATP2,3-
BPG And O2 metabolism Ann..N.Y.Acad.Sci.,1048:311-320.

Spasojević, I., Jelić S., Zakrzewska ,J., Bacić G.,2008 Decreased oxygen transfer capacity of erythrocytes as a
cause of 5-fluorouracil related ischemia. Molecules, 14:53-67. [PMID 19127237]

Stoll ,,M .Steckelings ,U.M., Paul, M., Bottari ,S.P. Metzger ,R.
Unger, T.,1995.
The angiotensin AT2-receptor mediates inhibition of
Cell proliferation in coronary endothelial cells
J. Clin .Invert, 95 ,651-657.

Tello,R. , Crewson ,P.E..,2003 .Hypothesis testing II:means.
J.Radiology .227: 1-4

Van Krimpen, C ,Smits. ,J.F.,Cleutjens ,J.P. Debets ,J.J.,Schoemaker ,R
.G. ,Struyker ,B.H.A.,Bosman,F.T.,Daemen, M.J.,1991.
DNA synthesis in the non-infacted cardiac interstitium
After left coronary artery ligation in the rat effect of
Captopril.
J. Mol .Cell .Cardial .23,1245-1253.

Yanase ,K.., Yoshiji,H., Ikenaka,Y.,Noguchi,R. Kitade,M . Kaji,K.Yoshii
,J.,Namisaki,T.,Yamazaki,M.Asada, K.Tsujimoto,T
Akahane ,T.,Uemura, M.,Fukui,H.,2007.

Synergistic inhibition of hepatocellular carcinoma Growth and hepatocarcinogenic by combination of 5-Fluorouracil and angiotensin-converting enzyme Inhibitor via anti-angiogenic activities . Oncol . Rep. .Feb , 17 (2): 441-446.

Yang, ,X.P. ,Liu ,Y.H. , Mehta ,D.,2001.Diminished carioprotective Response to inhibition of angiotensin-converting enzyme and angiotensin II type I receptor in B2 Kinin receptor knockout mice. Circ. Res ., 88: 1072 -1079.

Yun, F.F.,Yan ,X. , Zheng ,G.,2005.Areduction of endogenous asymmetric dimethylargnine contributes to the effect of captopril on endothelial dysfunction induced by homocysteine in rats. European J.of pharmacology 508, 167-175.

Zettner, A., Seligson ,D.,1964. Application of absorption spectrophotometery in Determination of calcium in serum. Clin. Chem . 10: 869-890 .