Clinical and Experimental Health Sciences

Investigation of the Effects of Amlodipine on Paracetamol-Induced Acute Kidney Toxicity in Rats

Erdogan Karatas[1], Zafer Bayraktutan[2], Elif Cadirci[1]

[1] Ataturk University, Faculty of Medicine, Department of Pharmacology, Erzurum, Türkiye.
[2] Ataturk University Faculty of Medicine, Department of Biochemistry, Erzurum, Türkiye.

Correspondence Author: Elif Cadirci
E-mail: ecadirci@atauni.edu.tr.

Received: 05.03.2021 **Accepted:** 22.10.2021

ABSTRACT

Objective: Paracetamol is an analgesic and antipyretic agent that widely used throughout the world. The increase of the usage and its easy accessibility brings along the toxicity risk. Paracetamol toxicity may result in drug induced hepatotoxicity and nephrotoxicity. Anti-inflammatory and antioxidant effects of amlodipine which creates vasodilatation by blocking L-type calcium channels and its usage in elderly for renoprotective purposes, ponders that it might be favorable in cases with inflammation such renal damage inducted with paracetamol. Thus, aim of our study is to analyze effects of amlodipine, one of L-type calcium channel blockers, in acute renal damage inducted with paracetamol.

Methods: 30 male rats consisting of 5 groups were used in our study. Groups; I: Health Control group. 2 ml Phosphate-buffered saline (PBS) oral was administered. II: 10 mg/kg Amlodipine III: Paracetamol (2g/kg) IV: 5 mg/kg Amlodipine + paracetamol V: 10 mg/kg Amlodipine + paracetamol. Rats were sacrificed after 24 hours following paracetamol administration.

Results: Serum levels of creatinine and blood urea nitrogen (BUN) were increased in paracetamol group, those parameters improved in amlodipine groups. While superoxide dismutase (SOD) activity and glutathione (GSH) levels measured in kidney decreased in paracetamol group, amlodipine has significantly corrected these parameters. Meanwhile malondialdehyde (MDA) quantities increased in paracetamol group, it has been seen that in the amlodipine administered groups quantities of increased MDA have statistically significantly decreased

Conclusion: This study showed that amlodipine has protective effects against paracetamol toxicity in kidney. Amlodipine revealed its protective effects by suppressing the oxidative damage and improving antioxidant activity. Amlodipine can be drug of choice in hypertensive patients with analgesic nephropathies.

Keywords: Amlodipine, kidney, paracetamol, rat, toxicity.

1. INTRODUCTION

Paracetamol is the most commonly used analgesic and antipyretic drug worldwide for the past 50 years, with few unwanted side effects when taken at therapeutic doses. Paracetamol is widely available over-the-counter or prescription. Increased use and easy accessibility bring with it the risk of toxicity (1, 2). Paracetamol taken at a dose of 200 mg/kg at one time in children over 6 years of age or 10 grams in total within 24 hours, and 200 mg/kg and above in a child under 6 years of age. leads to acute poisoning. In cases of increased sensitivity to paracetamol toxicity such as alcoholism, long-term fasting and isoniazid use, the toxic dose of paracetamol is 4 g per day or 100 mg/kg (2). Paracetamol toxicity may be asymptomatic, but it was shown in the early 1960s to cause drug-induced hepatotoxicity or more severe and fatal acute hepatic injury (3).

Paracetamol is ordinarily metabolized in the liver with conjugation reactions to achieve water soluble sulfate or glucuronic acid complexes. 2-4% of therapeutic doses of paracetamol is metabolized by the cytochrome p450 enzyme (CYP) to a toxic metabolite called N-acetyl p-benzoquinone (NAPQI). NAPQI is a highly reactive electrophilic molecule and bio-inactivated by binding with glutathione in the liver and then excreted in the urine (4, 5). When taken in toxic doses that is about 10-fold of therapeutic dose, the amount of NAPQI occurred exceeds the binding capacity of glutathione and this excess amount of NAPQI result in liver and kidney damage (6).

Paracetamol is converted to p-aminophenol metabolite in renal cortex, which is a selective nephrotoxic compound and causes necrosis at renal cortex by de-acetylation. P-aminophenol formed in therapeutic doses is conjugated with glutathione and excreted as inactive glutathione conjugates. In chronic use or at high doses, when glucuronide and sulphate conjugation pathways are saturated, glutathione stores are depleted and toxic NAPQI and p-aminophenol metabolites accumulate. The binding of NAPQI to the hepatocyte membrane and sulfhydryl proteins causes liver

DOI: 10.33808/clinexphealthsci.891902

damage. P-aminophenol binds to renal macromolecules by covalent bonds, causing kidney damage. Acetaminophen also has damaging effects on kidney medulla and papilla through prostaglandin (PG) synthase enzyme inhibition.

The calcium ion, which is generally responsible for the contraction relaxation responses in the body, is involved in all smooth and striated muscle functions. Calcium shows its cellular effects through calcium channels and many different calcium channels (L,T,P,Q etc.) have been defined according to its location. Amlodipine is one of the main antihypertensive agents that cause vascular dilatation by blocking L-type calcium channels (7). It is known that calcium blockers are preferred in diabetic patients to benefit from their kidney protective effects and because they increase cerebral blood flow in the elderly. Today, one of the most important effects of calcium channel blockers is its relaxing effect on vascular smooth muscle cells (8). This effect leads to increased renal circulation rate and glomerular filtration level. Unlike other vasodilators, calcium channel blockers do not cause water and salt retention. They also increase diuresis and natriuresis. It has been reported that these drugs prevent the drop-in glomerular filtration rate in hypertension and renal failure. Furthermore, promising results have been reported regarding its protective effects on acute tubular necrosis and acute renal failure due to renal ischemia or nephrotoxis (9). In previous studies, amlodipine's antihypertensive and renoprotective effects, as well as potent antioxidant and anti-inflammatory effects were reported (10-13). The fact that amlodipine has anti-inflammatory and antioxidant effects and is used for renoprotective purposes in the elderly is a condition with inflammation such as paracetamol-induced kidney damage. It suggests that it can also be useful in this situation.

In the light of above-mentioned literature, this study aimed to determine the effect of amlodipine, one of the L-type calcium channel blockers, in acute renal injury induced by paracetamol.

2. MATERIALS AND METHODS

2.1. Animals

A total of 30 Wistar Albino male rats, weighing 200-215 grams, obtained from the experimental animal laboratory within the Atatürk University Experimental Research and Application Center were used. During the experiment, the rats were given enough (ad libitum) water and pellet food. Animals were housed at normal room temperature (22 C ^{0}) in the laboratory and fed in groups before the experiment. All phases of our work have been approved by the Atatürk University Animal Experiments Local Ethics Committee (24.02.2012/2-26).

2.2. Experiment Plan

In the study, 5 animal groups each containing 6 rats, a total of 30 rats were used. All groups were fasted for 24 hours prior the experiment. Fasted animals were divided in the in the following groups:

Group I: Control group. 2 ml of 1X Phosphate-buffered saline (PBS) (containing 1% carboxymethyl cellulose-CMC) was administered orally by oral gavage.

Group II: Paracetamol solution prepared in 2 ml 1X Phosphate-buffered saline (PBS) (containing 1% carboxymethyl cellulose-CMC) at a dose of 2 g/kg was administered orally by gavage.

Group III: 1 hour after oral administration of 10 mg/kg amlodipine, 2 ml 1X Phosphate-buffered saline (PBS) (containing 1% carboxymethyl cellulose-CMC) was administered orally by oral gavage.

Group IV: 5 mg/kg amlodipine (2 ml of 0.9% NaCl prepared in solution) after 1 hour after oral administration of 2 g/kg dose of 2 ml paracetamol solution gavage was administered orally with.

Group V: 1 hour after oral administration of 10 mg/kg amlodipine, 2 ml paracetamol solution at a dose of 2 g/kg was administered orally by gavage.

All paracetamol doses administered in the study were adjusted according to the relevant literature (14). 4 hours after paracetamol administration, the rats in the whole group were given enough water (ad libitum) and feed until the end of the experiment.

The experiment was terminated by euthanasia with high dose thiopental (50 mg/kg) 24 hours after the administration of paracetamol to all groups. The kidneys and blood samples of the animals in all groups were taken. Part of the kidney removed was separated for biochemical analysis and placed in phosphate buffer and stored in a – 80 ˚C freezer. The remaining kidney histological studies % for 4s neutral was determined by placing the formaldehyde solution. The collected bloods were centrifuged and their serums were obtained and the serums were stored in a freezer – 80 °C.

2.3. Biochemical Studies

2.3.1. Analyzes Performed on Kidney Tissue

After the kidney tissues collected were stored at deep freezer and at the day of experiment they were homogenized with help of liquid nitrogen. 1 ml Phosphate-buffered saline (PBS) was added on 50 mg of kidney tissue and the mixture was homogenized in liquid nitrogen with Tissue Lyser II (Qiagen). Grounded tissue samples were centrifuged and supernatants were used for following analyses. Superoxide dismutase (SOD) activity (15) (Cayman Chemical Superoxide Dismutase Assay Kit Item Number 706002) glutathione (GSH) (16) (Cell Biolabs OxiSelect Total Glutathione (GSH) Assay Kit STA-312) and malondialdehyde (MDA) (17) (Cell Biolabs OxiSelect TBARS Assay Kit (MDA Quantitation) STA-330) levels were measured twice according to the modified methods with multi well plate reader in the light of the kit protocols (18, 19). Data were presented as the mean ± standard deviation

results per milligrams of protein. Total protein levels were analyzed by the Lowry Method (Sigma Aldrich, TP0300).

2.3.2. Analyses performed on Serum

The blood samples were taken into the tube without anticoagulant and centrifuged at 4000 g for 10 minutes. After the separated serum samples were transferred to Eppendorf tubes, they were placed in the device to be analyzed in the "Cobas C-501" auto analyzer. Renal function analyses were performed via commercial kits (BEN Biochemical Enterprise). Creatinine (Ref: Cr280) and BUN (Ref: BK151) levels were evaluated with multi well plate reader (20).

2.4. Statistical analysis

Results from the experiments were given as mean ± standard deviation, and P values below 0.05 were considered statistically significant. One – way variance analysis (ANOVA) following post-hoc "Duncan" test was used to determine significant differences between the groups.

3. RESULTS

3.1. Serum BUN and creatinine findings

As seen in Figures 1 and 2, the mean levels of BUN and creatinine levels in the serum of healthy rats were 14.4 ± 3.05 U/L and 0.25 ± 0.09 U/L, respectively, while in the control group given 2g/kg paracetamol, these levels were 27.25 ± 7.07 U/L and 0.65 ± 0.15 U/L, respectively. It was determined as L. In the control group given only 10 mg/kg amlodipine, BUN and creatinine levels were determined as 14.22 ± 2.49 U/L and 0.21 ± 0.13 U/L, respectively. The mean BUN and creatinine levels in rats given paracetamol + amlodipine 5 mg/kg were measured as 20.69 ± 4.26 U/L and 0.52 ± 0.06 U/L, respectively. BUN and creatinine levels in rats given paracetamol + amlodipine 10 mg/kg were measured as 18.25 ± 7.21 U/L and 0.4 ± 0.12 U/L, respectively.

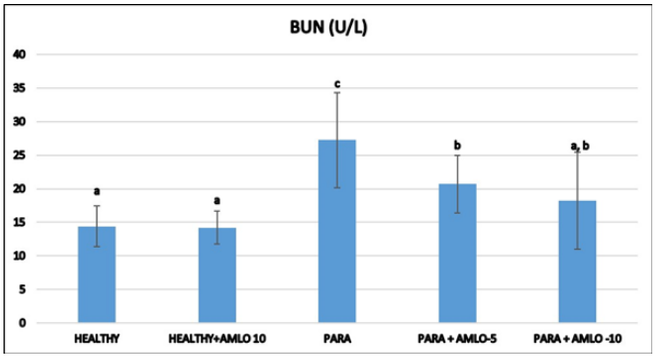

Figure 1. *Comparison of serum BUN levels according to groups Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

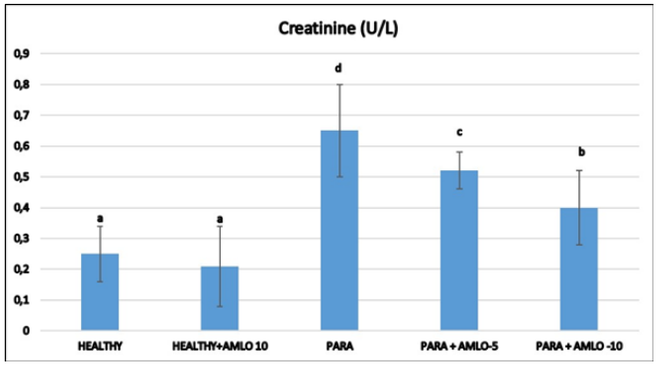

Figure 2. *Comparison of serum creatinine levels by groups Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

It was observed that the BUN value was significantly higher in the paracetamol group then the health rat group. It was observed that the BUN value in the PARA + AMLO5 group was lower than the paracetamol group and had approximately the same BUN values with the PARA + AMLO10 mg/kg and AMLO10 mg/kg groups.

When the creatinine levels were examined, it was observed that this value was significantly higher in the paracetamol group and there was a statistically significant difference compared to the other groups. Although there was no statistically significant difference between the PARA+AMLO 5 mg/kg, PARA+AMLO 10mg/kg and AMLO 10mg/kg groups, the best improvement in creatinine values were determined in the AMLO 10 mg/kg group.

3.2. Kidney SOD, GSH and MDA findings

As seen in Figures 3, 4 and 5, the mean levels of SOD, GSH and MDA in kidney tissue of intact rats were 30.33 ± 2.48 U/mg protein, 3.21 ± 0.57 nmol/mg protein and 1.42 ± 0.39 nmol/mg protein, respectively, while 2 g/kg paracetamol was given to the control group. These levels were determined as 14.52 ± 3. 94 U/mg protein, 1.21 ± 0.30 nmol/mg protein and 3.4 ± 0.86 nmol/mg protein, respectively. In the AMLO 10 group, these values were measured as 31.96 ± 4.40 U/mg protein, 3.26 ± 0.58 nmol/mg protein and 1.47 ± 0.32 nmol /mg protein, respectively. SOD, GSH and MDA levels in the PARA + AMLO 5 mg / kg group were 21.12 ± 4.72 U/mg protein, 2.26 ± 0.54 nmol/mg protein and 2.54 ± 0.43 nmol/mg protein, respectively, in the PARA + AMLO 10 mg/kg group. respectively 25.63 ± 5:56 U / mg protein, 26 ± 0.73 nmol / mg protein and 2.17 ± 0:33 nmol / mg protein was detected.

It was observed that there was a statistically significant difference in the SOD value in the paracetamol group and the other groups, and this value was significantly reduced. No significant difference was found between the PARA + AMLO 5 mg/kg and the PARA + AMLO 10 mg/kg groups.

GSH values measured in the paracetamol group were statistically significantly lower than the other groups. There was no significant difference in increasing GSH levels between

two different doses of amlodipine. The increase in GSH level observed in all treatment groups was parallel. Significantly, it was observed that AMLO application was quite effective in increasing GSH levels.

MDA level increased significantly in the paracetamol group. MDA levels significantly improved in the PARA + AMLO 5 and PARA + AMLO 10 treatment groups. The greatest improvement in terms of MDA level belonged to AMLO 10 mg/kg group.

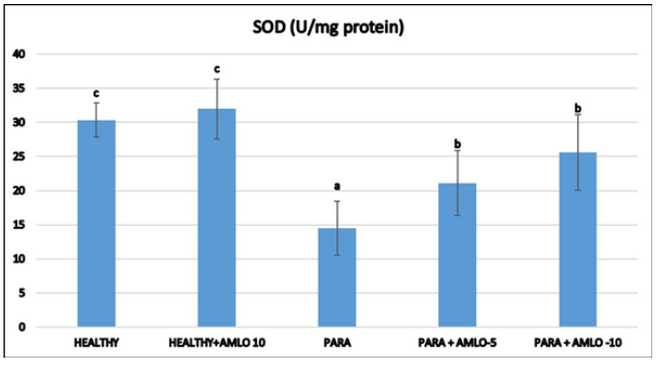

Figure 3. *Comparison of SOD levels in kidney tissue according to the groups. Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

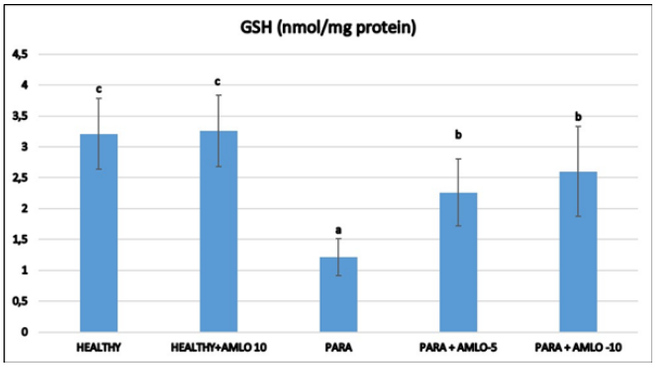

Figure 4.Comparison *of GSH levels in kidney tissue according to the groups. Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

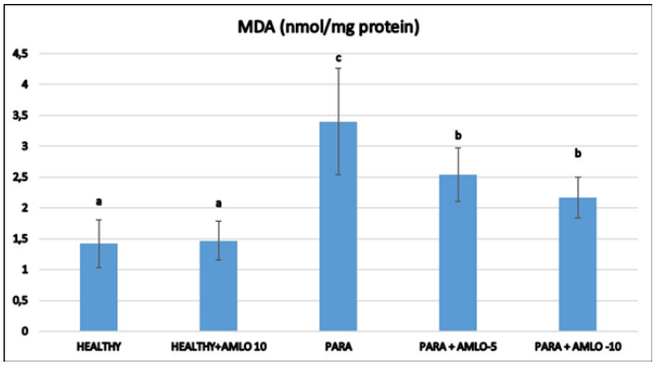

Figure 5. *Comparison of MDA levels in kidney tissue according to groups. Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

4. DISCUSSION

In this study, the effects of dihydropyridine derivative amlodipine, one of the L-type calcium channel blockers, on paracetamol toxicity induced experimentally in rat kidneys were demonstrated. For this purpose, BUN and CREATIN values, which are routine parameters of toxicity, and SOD, GSH and MDA values, which are oxidative stress and antioxidant system parameters, were examined.

Paracetamol is an analgesic and antipyretic drug and it is commonly used; even as an over the counter product. 90-95% of paracetamol, which administered at therapeutic concentrations, is conjugated to glucuronic acid, sulfuric acid, cysteine in the liver. Small amounts of hydroxylated and deacetylated metabolites of paracetamol it is excreted directly in the urine (21). A small part of paracetamol is transformed into n-acetyl-p-benzoquinone (NAPQI) by cytochrome-p mediated N-hydroxylation. NAPQI is a reactive intermediate, eliminated from the kidney by hepatic glutathione and detoxifying to the non-toxic acetaminophen-mercapturate compound. Paracetamol overdose causes severe hepatotoxicity as it is primarily metabolized in the liver. The kidneys, on the other hand, are affected in the advanced stages of liver damage or rarely alone, without liver damage (22).

Acute tubular necrosis can occur due to paracetamol overdose, and it has been found that approximately 1-2% of patients exposed to paracetamol overdose may develop renal failure (23). The mechanism of toxicity caused by paracetamol in the kidney has not been fully elucidated. In case of overdose, the cytochrome P-450 enzyme system is activated as a result of the saturation of glutathione and sulfation reactions. CYP2E1 isoenzyme is involved in biotransformation in the kidney. With the action of prostaglandin synthetase and N-deacetylase enzymes and cytochrome P-450 enzyme systems, toxic metabolites such as NAPQI and p-aminophenol are formed (2, 4). All of these metabolites cannot be detoxified and form conjugates with sulfhydryl and glutathione in cellular proteins. Glutathione depletion by these conjugates themselves or caused is thought to cause oxidative stress (24). It is thought that this situation leads to the activation of lysosomal enzymes and/or caspases, resulting in apoptosis or programmed cell death. As a result, hemostasis is disrupted, causing tissue damage, leading to impaired renal functions.

Measurement of BUN and creatinine levels in blood samples taken from patients has become routine in clinical evaluation of renal functions. In experimental studies, while evaluating kidney functions, BUN and creatinine levels were measured from animal sera, and the nephrotoxicity model created was evaluated and the effects of the drugs administered on kidney functions were examined (25, 26).

Naguib et al.(27) examined the fungus type Pleurotus ostreatus in hepatorenal damage caused by paracetamol. They observed that serum BUN and creatinine levels increased in the paracetamol group compared to the control group. In yet

another study, Das et al.(28) studied the effect of taurine on paracetamol-induced nephrotoxicity in mice. In evaluating the effects of oxidative damage on kidney functions, they based on BUN and creatinine levels and observed that these values increased. In our study, we used serum BUN and creatinine values to evaluate renal functions. We observed a statistically significant increase in serum BUN and creatinine levels 24 hours after the paracetamol group when compared with the healthy group. Based on this, we can say that our toxicity model occurs when we compare it with the healthy group. We see that amlodipine application, which we use as a treatment, improves kidney functions over these two values.

In a study conducted by Li et al.(29) the effects of amlodipine and nifedipine on gentanicin-induced kidney damage in rats were examined and both drugs were shown to reduce gentamicin-induced damage. Thus, the increased protein and N-acetyl-beta-D-glucosaminidase levels in the urine of rats and the increased amount of creatinine and BUN in the serum were decreased by these drugs. In the study, the authors examined both oxidative stress parameters and apoptosis pathways.(30) The beneficial effects of amlodipine in a kidney stone model made by Albayrak et al. Supports its protective effects in renal failure and damage (31). However amlodipine rat mesangial cells Smad6 and Smad7 upregulation with Adriamycin the toxicity overlapping studies and our findings inhibition of amlodipine supports the protective effect on kidney tissue (29).

NAPQI caused by the effect of CYP-450 enzyme systems is held responsible for paracetamol-induced kidney damage. During the detoxification of this electrophilic intermediate, different conjugates are formed with sulfhydryl and glutathione moieties in cellular proteins (4). It has been reported that these conjugates increase oxidative damage and this may be one of the toxicity mechanisms (24). In parallel with the increase in oxidative stress, the consumption of antioxidant defense systems is also important in paracetamol-induced kidney damage. The main reason for our study of amlodipine is its previously reported powerful antioxidant properties. Therefore, in our study, SOD and GSH were investigated as antioxidant parameters, and MDA, the biomarker of lipid peroxidation, as an oxidative parameter.

While SOD protects cells from the harmful effects of superoxide ion, GSH protects cells from oxidative damage by reacting with free radicals and peroxides. Abdul Hamid et al.(32) investigated the role of Zingiber zerumbet extract in paracetamol-induced nephrotoxicity and evaluated the resulting oxidative damage with the decrease in SOD and GSH levels. In our study, when we compared the SOD activity and GSH levels we used to evaluate oxidative damage, we observed a statistically significant decrease in the Paracetamol group compared to the healthy group. We see that our treatment group, the PARA + Amlodipine 5 and 10 mg/kg groups, showed a statistically significant increase compared to the paracetamol group. Considering our antioxidant parameters, we can say that amlodipine administration significantly reduces oxidative damage especially at a dose of 10 mg/kg.

Amlodipine and other dihydropyridine derivative calcium channel blockers are known for their powerful antioxidant effects (33). It has been shown in previous studies that amlodipine increases the amount of reduced glutathione in kidney tissue and increases the activity of superoxide dismutase enzymes (30). In another study, the protective effects of amlodipine, nifedipine, and nitrendipine on doxsurobicin – induced kidney damage were examined and only amlodipine was found to be effective. Amlodipine given at a dose of 5 mg/kg in the study improved the BUN and creatinine levels and also increased the GSH, SOD and GST values significantly (34). When these studies and our findings are evaluated together, it is clearly seen that amlodipine increases antioxidant parameters such as SOD and GSH in preventing kidney damage.

Superoxide radical and hydroxyl radical initiate lipid peroxidation in membranes of different cell organelles such as endoplasmic reticulum, nucleus, mitochondria and cytoplasm. MDA occurs in the peroxidation of fatty acids. MDA is found in blood and urine and correlates well with the degree of lipid peroxidation (35). Therefore, it is used in experimental studies. Aycan et al.(36) evaluated the effect of timoquinone on nephrotoxicity caused by paracetamol. They observed that lipid peroxidation decreased in the treatment group as a result of the measured MDA values. Also, previous studies demonstrated antioxidant effects of carvacrol and thymolare important against paracetamols harmful effects (37). As a result of our study, we observed that the MDA values in the paracetamol group increased significantly when compared to the healthy group. In the PARA + AMLODIPIN 5 and 10 mg/kg groups, the MDA level was close to the values of the healthy group. Considering the MDA levels in the PARA + AMLO 10 mg/kg group, we can say that it reduces lipid peroxidation and regresses it to an almost healthy level.

Li et al.(29) investigating the effects of amlodipine in a gentamicin-induced kidney injury model in rats, also demonstrated the contribution of amlodipine to decrease the amount of MDA in kidney tissue in preventing renal tubular damage. Again, the fact that amlodipine administration decreased kidney MDA levels in doxsurobicin-induced kidney toxicity supports the antioxidant effect of amlodipine and the protective effect of this effect on the kidneys (29).

5. CONCLUSION

In conclusion, in this study, we can say that amlodipine reduces paracetamol-induced kidney damage and this reduction is mediated by reducing oxidative stress and supporting antioxidant systems.

This finding suggests the use of amlodipine as an additional alternative to existing therapies, especially in the emergency treatment of paracetamol-induced renal toxicity. Also we can recommend amlodipine as a drug of choice in hypertensive

patients with analgesic nephropathies. However, more detailed experimental and clinical studies are needed to determine the current mechanism of action.

REFERENCES

[1] Canayakin D, Bayir Y, Kilic Baygutalp N, Sezen Karaoglan E, Atmaca HT, Kocak Ozgeris FB, et al. Paracetamol-induced nephrotoxicity and oxidative stress in rats: the protective role of Nigella sativa. Pharm Biol. 2016;54(10):2082-2091.

[2] Agrawal S, Khazaeni B. Acetaminophen Toxicity. StatPearls. Treasure Island (FL)2021.

[3] Davidson DG, Eastham WN. Acute liver necrosis following overdose of paracetamol. Br Med J. 1966;2(5512):497-499.

[4] Bessems JG, Vermeulen NP. Paracetamol (acetaminophen)-induced toxicity: molecular and biochemical mechanisms, analogues and protective approaches. Crit Rev Toxicol. 2001;31(1):55-138.

[5] Corcoran GB, Mitchell JR, Vaishnav YN, Horning EC. Evidence that acetaminophen and N-hydroxyacetaminophen form a common arylating intermediate, N-acetyl-para-benzoquinoneimine. Mol Pharmacol. 1980;18(3):536-542.

[6] Nguyen NU, Stamper BD. Polyphenols reported to shift APAP-induced changes in MAPK signaling and toxicity outcomes. Chem Biol Interact. 2017;277:129-136.

[7] Kayaalp SO. Akılcı tedavi yönünden tıbbi farmakoloji: Pelikan Yayıncılık; 2012 (Turkish).

[8] Bulsara KG, Cassagnol M. Amlodipine. StatPearls. Treasure Island (FL)2021.

[9] Schrier RW, Arnold PE, Van Putten VJ, Burke TJ. Cellular calcium in ischemic acute renal failure: role of calcium entry blockers. Kidney Int. 1987;32(3):313-321.

[10] Albayrak A, Bayir Y, Halici Z, Karakus E, Oral A, Keles MS. The biochemical and histopathological investigation of amlodipine in ethylene glycol-induced urolithiasis rat model. Ren Fail. 2013;35(1):126-131.

[11] Coskun AK, Gunal A, Halici Z, Oral A, Seyrek M, Bayir Y. The effects of amlodipine on the biochemical and histopathological changes in the rabbit ileum subjected to ischemia-reperfusion. Eurasian J Med. 2011;43(1):33-38.

[12] Halici Z, Karaca M, Keles ON, Borekci B, Odabasoglu F, Suleyman H. Protective effects of amlodipine on ischemia-reperfusion injury of rat ovary: biochemical and histopathologic evaluation. Fertil Steril. 2008;90(6):2408-2415.

[13] Suleyman H, Halici Z, Hacimuftuoglu A, Gocer F. Role of adrenal gland hormones in antiinflammatory effect of calcium channel blockers. Pharmacol Rep. 2006;58(5):692-699.

[14] Chattopadhyay RR. Possible mechanism of hepatoprotective activity of Azadirachta indica leaf extract: part II. J Ethnopharmacol. 2003;89(2-3):217-219.

[15] Sun Y, Oberley LW, Li Y. A simple method for clinical assay of superoxide dismutase. Clinical Chemistry 1988;34(3):497-500.

[16] Sedlak J, Lindsay RH. Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Analytical Biochemistry 1968; 25(1):192-205.

[17] Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Analytical Biochemistry 1979;95(2):351-358.

[18] Bayir Y, Un H, Cadirci E, Akpinar E, Diyarbakir B, Calik I. Effects of Aliskiren, an RAAS inhibitor, on a carrageenan-induced pleurisy model of rats. Anais da Academia Brasileira de Ciências 2019;91(1): e20180106.

[19] Karaoglan ES, Bayir Y, Albayrak A, Toktay E, Ozgen U, Kazaz C. Isolation of Major Compounds and Gastroprotective Activity of Alchemilla Caucasica on Indomethacin Induced Gastric Ulcers in Rats. Eurasian J Med. 2020;52(3):249-253.

[20] Un H, Ugan RA, Kose D, Bayir Y, Cadirci E, Selli J. A novel effect of Aprepitant: Protection for cisplatin-induced nephrotoxicity and hepatotoxicity. Eur J Pharmacol. 2020;880:173168.

[21] Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman & Gilman's the pharmacological basis of therapeutics: McGraw-Hill Education New York; 2018.

[22] Ozkaya O, Genc G, Bek K, Sullu Y. A case of acetaminophen (paracetamol) causing renal failure without liver damage in a child and review of literature. Renal Failure 2010;32(9):1125-1127.

[23] Prescott LF. Paracetamol overdosage-Pharmacological considerations and clinical management. Drugs 1983;25(3):290-314.

[24] Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. J Med Toxicol. 2008;4(1):2-6.

[25] El-Sayed EM, Abd-Allah AR, Mansour AM, El-Arabey AA. Thymol and carvacrol prevent cisplatin-induced nephrotoxicity by abrogation of oxidative stress, inflammation, and apoptosis in rats. J Biochem Mol Toxicol. 2015;29(4):165-172.

[26] Somchit MN, Sanat F, Hui GE, Wahab SI, Ahmad Z. Mefenamic Acid induced nephrotoxicity: an animal model. Adv Pharm Bull. 2014;4(4):401-404.

[27] Naguib YM, Azmy RM, Samaka RM, Salem MF. Pleurotus ostreatus opposes mitochondrial dysfunction and oxidative stress in acetaminophen-induced hepato-renal injury. BMC Complement Altern Med. 2014;14:494.

[28] Das J, Ghosh J, Manna P, Sil PC. Taurine protects acetaminophen-induced oxidative damage in mice kidney through APAP urinary excretion and CYP2E1 inactivation. Toxicology. 2010;269(1):24-34.

[29] Li J, Tie CR, Li QX, Zheng F. Amlodipine prevents adriamycin-induced toxicity in cultured rat mesangial cells by up-regulation of Smad6, Smad7 expression. Environ Toxicol Phar. 2014;38(1):251-256.

[30] Tan H, Gepdiremen A, Halici Z. Effect of lithium and valproic acid on kainate-induced neurotoxicity in cerebral cortical cell. Asian J Chem. 2009;21(3):1769-1774.

[31] Albayrak A, Bayir Y, Halici Z, Karakus E, Oral A, Keles MS. The biochemical and histopathological investigation of amlodipine in ethylene glycol-induced urolithiasis rat model. Febs J. 2013;280(S1):336-337.

[32] Abdul Hamid Z, Budin SB, Wen Jie N, Hamid A, Husain K, Mohamed J. Nephroprotective effects of Zingiber zerumbet Smith ethyl acetate extract against paracetamol-induced nephrotoxicity and oxidative stress in rats. J Zhejiang Univ Sci B. 2012;13(3):176-785.

[33] Cominacini L, Fratta Pasini A, Garbin U, Pastorino AM, Davoli A, Nava C, et al. Antioxidant activity of different dihydropyridines. Biochem Biophys Res Commun. 2003;302(4):679-84. 176-185.

[34] Liu LL, Li QX, Xia L, Li J, Shao L. Differential effects of dihydropyridine calcium antagonists on doxorubicin-induced nephrotoxicity in rats. Toxicology. 2007;231(1):81-90.

[35] Nielsen F, Mikkelsen BB, Nielsen JB, Andersen HR, Grandjean P. Plasma malondialdehyde as biomarker for oxidative stress: Reference interval and effects of life-style factors. Clin Chem. 1997;43(7):1209-1214.

[36] Aycan IO, Tokgoz O, Tufek A, Alabalik U, Evliyaoglu O, Turgut H. The use of thymoquinone in nephrotoxicity related to acetaminophen. Int J Surg. 2015;13:33-37.

[37] Palabiyik SS, Karakus E, Halici Z, Cadirci E, Bayir Y, Ayaz G. The protective effects of carvacrol and thymol against paracetamol-induced toxicity on human hepatocellular carcinoma cell lines (HepG2). Hum Exp Toxicol. 2016;35(12):1252-1263.

How to cite this article: Karatas E, Bayraktutan Z, Cadirci E. Investigation of the Effects of Amlodipine on Paracetamol-Induced Acute Kidney Toxicity in Rats. Clin Exp Health Sci 2022; 12: 155-161. DOI: 10.33808/clinexphealthsci.891902