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The Effects of Artemisinin on Oxidative Stress Markers in Mouse Heart and Lung Tissues in an Experimental Model of Epileptic Seizure

Deneysel Epileptik Nöbet Modelinde, Artemisinin'in Fare Kalp ve Akciğer Dokularında Oksidatif Stress Belirteçleri Üzerine Etkisi

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Abstract

Aim: The current study investigated the effects of artemisinin on the heart and lung tissue against pentylenetetrazol-induced seizures in mice. For this purpose, malondialdehyde (MDA), advanced oxidation protein products (AOPP), Catalase (CAT), glutathione (GSH), and glutathione peroxidase (GSH-Px) levels were evaluated in both tissue homogenates.

Material and Method: Swiss albino male mice (n=42) were used in the experiment. Animals were divided into six groups: Control (C), pentylenetetrazol (PTZ), valproate 100 mg/kg (VPA), artemisinin 30 mg/kg (ARS), + PTZ, ARS 60 mg/kg+PTZ, and ARS 120 mg/kg+PTZ. On the 26th day of the experiment, the mice were sacrificed and the samples were kept at -80 0C for biochemical analysis.

Results: There were significant differences in the five biochemical parameters analyzed in heart and lung tissues. Heart and lung MDA levels of the PTZ group were significantly higher than the C and ARS-60 groups ($p<0.05$). Likewise, heart AOPP levels decreased significantly in the VPA and ARS-60 groups compared to the PTZ group ($p<0.05$). There was no significant difference between the groups regarding lung AOPP levels ($p>0.05$). Heart CAT and GSH levels decreased in the PTZ group compared to the other groups. However, regarding lung CAT levels, the PTZ group had the highest value compared to the other groups, while it had the lowest value in terms of GSH level. The GSH-Px level did not differ significantly between the groups in heart tissue ($p>0.05$). The lung GSH-Px level significantly increased in the ARS-30 group when compared to the PTZ group ($p<0.05$).

Conclusion: The findings suggest that ARS treatment can inhibit PTZ-induced oxidative stress in peripheral tissues and ARS may provide improvements in decreased antioxidant enzymes and contribute to the antioxidant defense system.

Keywords: Artemisinin, pentylenetetrazol, oxidative stress, antioxidant, heart, lung

Öz

Amaç: Mevcut çalışma, farelerde pentilentetrazol indüklenen nöbetlere karşı artemisinin'in kalp ve akciğer dokusundaki etkileri araştırılmıştır. Bu amaçla her iki doku homojenatında malondialdehit (MDA), ileri oksidasyon protein ürünleri (AOPP), Katalaz (KAT), glutatyon (GSH) ve glutatyon peroksidaz (GSH-Px) düzeyleri değerlendirilmiştir.

Gereç ve Yöntem: Deneyde Swiss albino erkek fareler (n=42) kullanıldı. Hayvanlar Kontrol (C), pentilenetetrazol 35 mg/kg (PTZ) , valproat 100 mg/kg (VPA), artemisinin 30 mg/kg (ARS),+ PTZ, ARS 60 mg/kg+PTZ, ARS 120 mg/kg+PTZ olmak üzere altı gruba ayrıldı. Deneyin 26. gününde farelrer sakrifiye edilerek, biyokimyasal analizler için numuneler -80 0C'de muhafaza edildi.

Bulgular: Kalp ve akciğer dokularında analiz edilen beş biyokimyasal parametrede anlamlı farklar vardı. PTZ grubunun, Kalp ve akciğer MDA düzeyleri C ve ARS-60 grubuna göre anlamlı olarak yüksek bulundu ($p<0.05$). PTZ grubunun, Kalp ve akciğer MDA düzeyleri C ve ARS-60 grubuna göre anlamlı olarak yüksek bulundu. Aynı şekilde kalp'te AOPP düzeyleri VPA ve ARS-60 gruplarında anlamlı bir azalış sergilerken ($p<0.05$). akçiğerde ise gruplar arasında anlamlı bir fark yoktu ($p>0.05$). PTZ grubunun kalp'te CAT ve GSH düzeyleri diğer gruplara göre azalırken, akciğerde CAT düzeyi artığı, GSH düzeyininde azaldığı bulundu. Kalp dokusundaki GSH-Px düzeyinde gruplar arasında anlamlı bir fark bulunmadı ($p>0.05$). GSH-Px düzeyi, akciğerde sadece ARS-30 grubunda anlamlı artış göstermiştir ($p<0.05$).

Sonuç: Sonuç olarak, PTZ uygulanan farelerde oluşan nöbetlerin periferal dokularda oksidatif strese neden olur. ARS ön tedavisi PTZ kaynaklı periferik dokularda oluşabilecek oksidatif stresi inhibe edebilir. Ayrıca ARS azalan antioksidan enzimler üzerinde iyileşmeler sağlayabilir ve antioksidan savunma sistemine katkıda bulunabilir.

Anahtar Kelimeler: Artemisinin, pentilentetrazol, oksidatif stres, antioksidan, kalp, akciğer

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INTRODUCTION

Epilepsy is one of the neurological diseases that may affect society. It is a type of disease characterized by recurrent seizures. It is idiopathic because its mechanism is not fully understood.[1] Researchers have suggested that epilepsy may occur due to brain damage, infections, stroke, and congenital anomalies.[2] In recent studies, it has been reported that damage to the brain and other organs of the body caused by oxidative stress will trigger epileptic seizures and play a role in the pathogenesis of epilepsy. Oxidative stress is the formation of tissue damage by the degeneration of cells by lipid peroxidation and Advanced oxidation protein products (AOPP) resulting from the excessive production of free radicals. As a result, malondialdehyde (MDA), the end product of lipid peroxidation, increases, which causes a decrease in the levels of antioxidants such as catalase (CAT), glutathione (GSH), and glutathione peroxidase (GSH-PX).[3-5]

Pentylenetetrazol (PTZ) is an agent used as a respiratory and circulatory system stimulant. This agent, which was used to treat mental disorders in the past, was later banned because it had side effects such as uncontrollable convulsions. The mechanism by which PTZ causes these convulsions is still not understood. However, it is used to create convulsions in experimental epilepsy models because it creates seizures similar to those in epilepsy.[6]

It has been reported that epilepsy may affect the cardiovascular system and cause extensive ischemia. Mortality due to epileptic seizures is associated with cardiac arrhythmia and sudden cardiac arrest. In addition, edema in the lungs, congestion, and bleeding in the alveoli have been reported as the cause of sudden death in epilepsy.[7]

Valproate (VPA) is one of the antiepileptic drugs used to treat epilepsy. This drug, which has widespread clinical use, is experimentally used as an anticonvulsant agent in epilepsy models. Although the antiepileptic mechanism of action of VPA is not fully known, it has been reported that it acts by modulating sodium channels.[8]

Artemisinin (ARS) is a compound found in the plant Artemisia annua, which grows in the Asian continent. This compound is widely used to treat malaria. It is also reported that ARS has antioxidant, anticancer, antimicrobial, and anti-inflammatory activity.[9-11] In addition, the antioxidant capacity of ARS was evaluated in vitro by the 2,2-Diphenyl-1-picrylhydrazyl hydrate (DPPH) method and it was found that it has free radical scavenging activity.[10] ARS suppresses oxidative stress due to epileptic seizures in the PTZ-Kindling model and exhibits antioxidant and antiapoptotic effects.[12] ARS derivatives have been reported to antagonize N-methyl-D-aspartate (NMDA) receptors. Activation of the NMDA receptor has been found to increase oxidative stress in neurons. In addition, inhibition of the NMDA receptor showed a reducing effect on oxidative stress parameters. Thus, the above-mentioned mechanism of action of ARS was considered in the current study, and the effects of ARS against oxidative stress in the circulatory and respiratory system organs due to epileptic seizures were examined.[13,14]

In light of the information provided above, in this study, we focused on the effects of ARS pretreatment on the heart and lung tissue against oxidative stress that may occur due to PTZ. We evaluated these effects regarding MDA, CAT, GSH, GSH-Px, and AOPP.

MATERIAL AND METHOD

Ethical Declaration

This study was conducted after obtaining ethical approval of the local ethics committee of Van Yuzuncu Yil University (decision date 28.07.2022 and numbered 13).

Animals and Experimental Desing

Swiss albino male mice, two months old and weighing 20-25 g, were used in this study. Animals were housed in standard plastic cages and acclimated to 12-hour light, and 12-hour dark cycles at room temperature. All animals were fed with tap water and pellet chow.

Animals (Group 1; C/saline, Group 2; PTZ (35 mg/kg)+PTZ, Group 3; VPA (100 mg/kg)+PTZ, Group 4; ARS (30 mg/kg)+PTZ, Group 5 ARS (60 mg/kg)+PTZ, and Group 6; ARS (120 mg/kg)+PTZ) were divided into six groups. After completion of the experiment, all animals were sacrificed. Heart and lung tissues were taken and kept at -80°C for this study.

PTZ-Kindling Model

PTZ-Kindling is a chronic epileptic condition that causes convulsions in animals at repeated doses. The PTZ-Kindling method was applied with minor modifications, inspired by a previous study.[15] PTZ (35 mg/kg) sub-convulsive dose was administered intraperitoneally to Test groups (Groups 2, 3, 4, 5, and 6) every other day. Mice received 11 injections up to day 24 of the experiment. Doses of VPA (100 mg/kg) and ARS (30, 60, and 120 mg/kg) were administered before PTZ. Mice were administered a PTZ-threatening (75 mg/kg) dose on the last day of the experiment (day 26).[15]

Preparation of Homogenates of Mouse Heart and Lung Tissues

Heart and kidney tissues were homogenized by placing them in phosphate buffer saline with pH 7.4. It was then centrifuged at 10,000 rpm for 20 minutes. The resulting supernatant was stored at -80°C.

Biochemical Analysis

Heart and lung tissue MDA levels,[16] CAT activity,[17] GSH levels,[18] GSH-Px[19] and AOPP level[20] were measured spectrophotometrically.

RESULTS

MDA levels were measured in the heart and lung tissue of the mice. According to the results, there was a significant increase in heart tissue in the PTZ group compared to the C, VPA, and ARS-60 groups ($p<0.05$). Given the MDA levels in the lung tissue homogenate, ARS-30 and ARS- 60 groups decreased MDA levels compared to the PTZ group ($p<0.05$). In both tissues, the ARS-120 group did not show a significant decrease compared to the PTZ group ($p>0.05$). While the VPA group decreased the MDA level in the heart tissue, it did not show a significant decrease in the lung tissue. Heart and lung tissue MDA levels are shown in **Figure 1**.

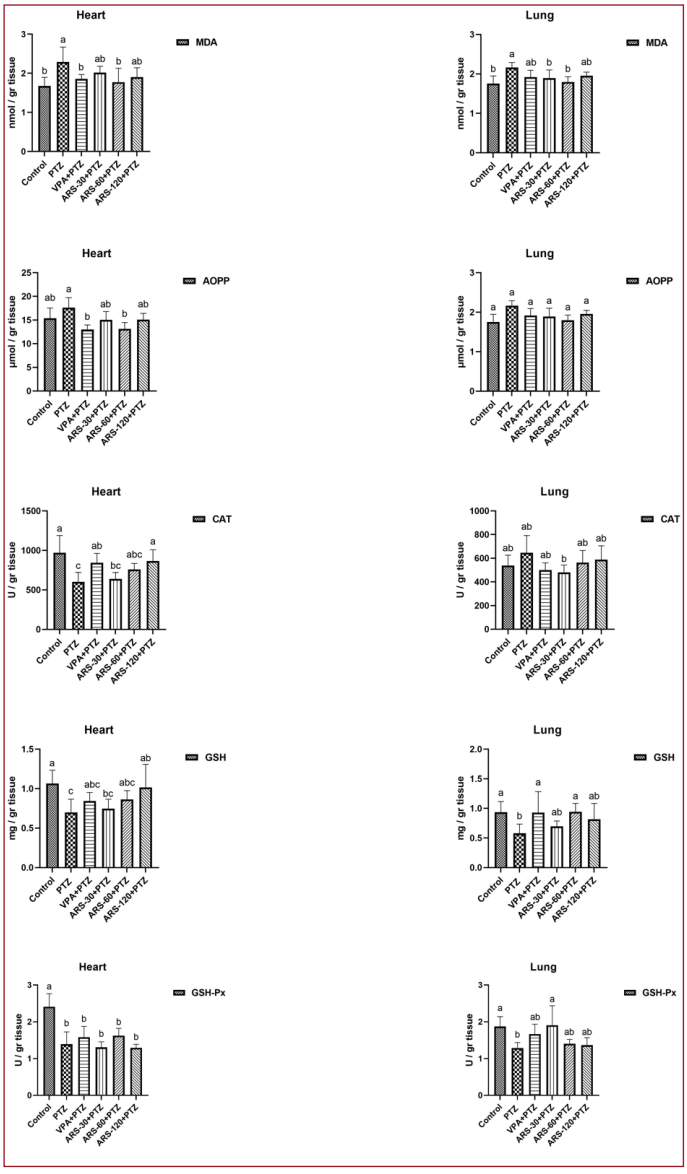

Figure 1. Comparison of the values of parameters measured in Heart and Lung homogenates. *Different letters in the same column represent statistical significance ($p<0.05$). Values are shown as mean ± SD. n = 7 animals per group. PTZ: pentylenetetrazol, VPA: Valproate, ARS: Artemisinin, MDA: Malondialdehyde, CAT: Catalase, GSH: Glutathione, GSH-Px: Glutathione peroxidase, AOPP: Advanced oxidation protein products.

AOPP levels in heart and lung homogenates were demonstrated in **Figure 1**. In heart tissue homogenate, PTZ administration caused an increase in AOPP levels in the groups. However, when group C was compared with other groups, there was no significant difference ($p>0.05$). In addition, the VPA and ARS-60 groups showed a significant decrease compared to the PTZ group ($p<0.05$). When the lung tissue was examined, no significant difference was found between all groups ($p>0.05$).

CAT levels were also measured in the heart. C, VPA, and ARS-120 groups increased compared to the PTZ group ($p<0.05$). CAT levels did not increase significantly in the ARS-30 and ARS-60 groups compared to the C and PTZ groups ($p>0.05$). There was no significant difference between the groups in CAT levels in lung tissue ($p>0.05$). However, the CAT level of the ARS-30 group was lower than the other groups (**Figure 1**).

GSH levels are shown in **Figure 1**. GSH values of the PTZ group decreased in heart and lung tissue due to seizures due to PTZ. C and ARS-120 groups showed a significant increase in heart tissue compared to the PTZ group ($p<0.05$). In addition, lung homogenate showed an increase in C, VPA, and ARS-60 groups compared to the PZT group ($p<0.05$).

GSH-Px levels did not show a significant increase in heart tissue ($p>0.05$). The findings showed PTZ group C decreased compared to the control group. C and ARS-30 groups increased in the lung compared to the PTZ group ($p<0.05$). There was no significant difference between the other groups regarding GSH-Px level ($p>0.05$, **Figure 1**).

DISCUSSION

Seizures in epilepsy may cause stress on the organs of the circulatory system (Heart and Lung).[21] In addition, these seizures cause respiratory disorders, and lung damage and affect oxygen delivery to peripheral organs. This may bring about oxidative stress and cellular damage in tissues.[22,23] In this study, epileptic seizures were induced by PTZ. We examined the effects of ARS pretreatment on oxidative stress parameters and antioxidant enzymes that may develop due to seizures in heart and lung tissue. Results of the current study showed that low and medium doses of ARS were more effective on biochemical parameters than the PTZ group. The high dose of ARS was ineffective. This limits the therapeutic dose range of ARS. In addition, the medium dose of ARS suppressed oxidative stress markers in heart and lung tissue and was better at regulating antioxidant enzymes than VPA. NMDA receptors are known for their function in neurons and their role in the pathophysiology of epilepsy.[13,24] However, studies on its presence in the lung and other tissues are limited. A recent study identified lung smooth muscle cell types that express NMDA receptors. These cells have been reported to cause constrictions in the airway by activating the NMDA receptor.[24,25] ARS has an antagonistic effect on NMDA receptors. It has also been reported that the blockade of the NMDA receptor prevents oxidative stress.[13,14] Therefore, ARS

suggests that its effects on oxidative stress on lung and heart tissue may be due to its suppression of NMDA receptors and antioxidant capacity.

Lipid peroxidation, which occurs together with oxidative stress, causes the formation of MDA. It is toxic to cells and causes tissue damage.[26] Previous studies have reported that PTZ administration triggers lipid peroxidation in the organism and increases MDA.[27,28] ARS medium dose was more effective than the PTZ group in terms of MDA level in heart tissue. Likewise, low and medium doses of ARS showed efficacy by reducing the MDA level in the lung tissue. A high dose of ARS was not effective in both tissues. While VPA decreased MDA in heart tissue, it did not make a significant difference in the lung compared to the PTZ group. ARS and its derivatives are reported to act by inhibiting inflammation and oxidative stress in respiratory tract disorders.[8] In a study with ARS derivatives, they found that it prevented acute lung damage and inhibited MDA levels.[29] It has been reported that ARSs suppress MDA levels in Renal Ischemia Reperfusion-Induced Lung Inflammation.[30] In addition, it has been reported that it reduces MDA levels by suppressing oxidative stress in ARS diabetic nephropathy rats and provides a renal protective effect.[31] It has been determined that ARS can scavenge free radicals and therefore may have antioxidant activities.[10] In this study, the effects of ARS on MDA levels in respiratory and circulatory system organs suggests that ARS may be related to its antioxidant capacity and inhibitory effects on oxidative stress.

AOPPs are biomarkers of tissue damage and inflammation that may occur due to oxidative stress. Oxidation proteins play a role in the pathophysiology of many diseases by triggering oxidative stress.[31-33] AOPPs show a similar correlation with an increase as does MDA, the end product of lipid peroxidation.[32] Our study model is unique for assessing heart and lung tissue AOPP levels. Findings, PTZ has been reported to increase AOPP levels in peripheral organs.[23,33] PTZ increased the level of AOPP in heart tissue, but did not make a significant difference in the lung. In heart tissue, the VPA and ARS-60 groups reduced AOPP relative to both the C and PTZ groups. The antioxidant activity of ARS is known.[10] In addition, the protective efficacy of ARS against cardiac toxicity has been reported in previous studies.[34] The results of AOPP in heart tissue suggest that ARS may have a suppressive effect on oxidation proteins, possibly with a mechanism of action similar to the studies mentioned above.

Antioxidants play an important role in scavenging free radicals in the body. CAT, GSH, and GSH-PX are the main antioxidants that protect the defense system of the organism.[35] CAT is one of the antioxidant defense systems that protect the organism from the harmful effects of hydrogen peroxide.[36] It has been reported in previous studies that PTZ reduces CAT levels.[37,38] In this study, it was observed that there was a decrease in the groups treated with PTZ compared to the control group, and it was determined that ART treatment increased the CAT level in the heart tissue in a dose-dependent manner. This shows that ART can contribute to the antioxidant defense system and has the potential to prevent PTZ-induced oxidative stress. The body's impaired antioxidant defense system can cause oxidative stress. In addition, disruption of this defense system may trigger epileptic seizures. As a result, it can contribute to lung degeneration and dysfunction.[21,39] In our study, CAT levels in the PTZ group in the lung tissue increased significantly compared to the control and treatment groups. The findings of our study are compatible with the literature.[21] This situation shows the increase of excessive free radicals originating from PTZ, which suggests the protection reflex by increasing the enzymes such as CAT in the antioxidant defense system of the cell against the oxidative stress that develops accordingly.

GSH and GSH-Px are enzymes of the antioxidant defense system that act together to prevent reactive oxygen derivatives from damaging the cell.[40] In this study, PTZ reduced GSH and GSH-Px levels in heart and lung homogenates. It suggests that ARS and VPA pretreatment increase GSH levels in heart and lung tissue and may reduce PTZ-induced oxidative stress. While ART application was not effective in the heart tissue regarding GSH-Px level, ARS was effective at low doses in the lung. Our findings are in agreement with the literature.[41-43] In previous studies, it has been reported that PTZ application triggers seizure formation by increasing oxidative stress and may cause damage to peripheral tissues.[23,44] To our knowledge, no studies were found investigating the effect of ARS on GSH, GSH-Px enzymes. However, it was reported that Artemisia annua extract, from which ARS was isolated, increased the decreased GSH and GSH-Px levels in rats treated with DMBA (7,12-dimethylbenz[a]anthracene) and exhibited antioxidant activity.[45] In lung tissue, low and medium doses of ARS partially increased GSH and GSH-Px levels compared to the PTZ group, while only the high dose was effective in heart tissue. This result can be attributed to the partial effect of ARS on GSH and GSH-Px levels and its ability to maintain the oxidant/antioxidant balance.

CONCLUSION

The findings obtained in this study suggest that seizures in mice induced by PTZ could increase oxidative stress in brain tissue and peripheral tissues such as the heart and lungs. Thus, the damage that seizures may cause in peripheral organs should be considered. Against PTZ toxicity, ARS pretreatment reduced oxidative stress parameters in both organs. Especially the medium dose of ARS was more effective. VPA was more effective in preventing oxidative stress in heart tissue. In addition, ARS showed improvements in antioxidant parameters. As a result, ARS can reduce oxidative stress and contribute to the antioxidant defense system. However, more detailed experimental studies are should be conducted to elucidate the mechanism of action of ARS on peripheral organs.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was conducted with the approval of the local ethics committee of Van Yüzüncü Yıl University (decision date 28.07.2022 and numbered 13).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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