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Research Article
Dose-Dependent Pulmonotoxic Effects of Favipiravir in Rats Biochemical and Histopathological Evaluation

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Abstract

Background and Objective: Favipiravir is associated with more serious side effects at higher doses. This experimental study proposed to investigate the effect of favipiravir on dose-dependent lung toxicity in rats biochemically and histopathologically. **Materials and Methods:** The rats were divided into four groups as healthy (HG), 100 mg/kg favipiravir (FAV-100), 200 mg/kg favipiravir (FAV-200) and 400 mg/kg favipiravir (FAV-400). Favipiravir 100, 200 and 400 mg/kg doses were administered by oral gavage to the other groups except HG. To the HG group, only distilled water (0.5 mL) was applied in the same way. This procedure was repeated twice a day for a week. Then, the rats were euthanised with high-dose anaesthesia and lung tissues were removed. Oxidative stress parameters such as malondialdehyde (MDA), Total Glutathione (tGSH), superoxide dismutase (SOD), total oxidant status (TOS) and total antioxidant status (TAS) were examined. After the one-way ANOVA, the Tukey's *post hoc* test was performed. **Results:** Favipiravir dose-dependently increased MDA and TOS also decreased tGSH, SOD and TAS in rat lung tissue. As favipiravir was given in increasing doses, it was easier to observe the changes between the different groups. This was also supported by the histopathological data. Histopathologically, interstitial pneumonia and lymphoid hyperplasia were mild in the 100 mg/kg favipiravir group, severe at high doses. **Conclusion:** As the dose of favipiravir increased, oxidant levels increased and antioxidant levels decreased in the lung tissue. In line with these results, it was observed that favipiravir caused a dose-dependent pulmonotoxic effect in rats.

Key words: Interstitial pneumonia, Favipiravir, lung, albino Wistar, hyperplasia, lymphoid hyperplasia, oxidative damage, antioxidant depletion, antiviral therapy

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Favipiravir is a nucleoside-derived prodrug with a broad antiviral spectrum that is an inhibitor of viral RNA-dependent RNA polymerase[1]. It is converted to its active form, favipiravir-ribofuranosyl-5'-triphosphate, by phosphoribosylation and phosphorylation in tissue[2]. Favipiravir was licensed for use against influenza virus in Japan, then it was found to be effective against many RNA viruses including Ebola, Norovirus and Enterovirus[3]. High doses of favipiravir have been advised for use in COVID-19 infections because of its antiviral activity against Ebola and SARS-CoV-2[4]. Unfortunately, high doses of favipiravir cause more serious side effects[5]. It is stated that the most common side effects during favipiravir use are diarrhoea, nephrotoxicity, increased serum uric acid and transaminase levels and decreased white blood cell and neutrophil levels. Less frequently, nausea, vomiting, abdominal pain, skin rash, itching, delirium, hallucinations and convulsions are observed[6,7]. Severe and fatal side effects have been reported to occur more frequently in men and those over 64 years of age[8]. In addition, favipiravir has been documented to be teratogenic in multiple species and contraindicated in pregnancy[9]. The effect of favipiravir on reproductive dysfunction has been associated with oxidative stress[10]. In recent years the increasing use of favipiravir and oxidative stress and genotoxicity have been reported as two important indicators of drug-induced toxicity[11]. In a recent experimental study, it was reported that favipiravir caused hepatotoxicity by increasing malondialdehyde (MDA) levels and decreasing endogenous antioxidant levels such as glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) in the liver[12]. Bilici *et al.*[13] showed that favipiravir-induced oxidative and inflammatory liver damage was aggravated with increasing dose. Information from the literature indicates that favipiravir remains a safety concern[5]. It also suggests that reactive oxygen species (ROS) are involved in the pathogenesis of favipiravir-related injury. In the literature, it is not known the toxic effect of increasing doses of favipiravir in the lungs. Therefore, the purpose of the current study is to investigate the relationship between the severity of possible oxidative damage and drug dose administered increasing doses of favipiravir in the lung tissue of rats biochemically and histopathologically.

MATERIALS AND METHODS

Study area: This study was carried out at Erzincan Binali Yildirim University, Faculty of Medicine, Erzincan, Türkiye from January to February, 2023.

Animals: A total of 24 male albino Wistar rats weighing between 280-290 g were used in the experiment. All rats were collected from the Animal Application and Research Centre, Erzincan Binali Yildirim University, Turkey. Before the experiment, the animals were kept in the laboratory room at room temperature (22°C), 12 hrs light and 12 hrs dark for one week to adapt to the environment. During this period, rats were provided with normal animal feed and tap water *ad libitum*.

Ethical consideration: All stages of the study were carried out with ethical principles and accepted by the Erzincan Binali Yildirim University Animal Experiments Local Ethics Committee on February 07, 2022 (Decision No: 1/8).

Chemical substances: The favipiravir (200 mg) was obtained from the Ministry of Health (Türkiye) and thiopental sodium (0.5 g) from Ibrahim Etem Ulagay (Türkiye).

Animal groups: The rats were randomly divided into four groups (n = 6) as healthy (HG), 100 mg/kg favipiravir (FAV-100), 200 mg/kg favipiravir (FAV-200) and 400 mg/kg favipiravir (FAV-400).

Experiment procedure: First, favipiravir 100, 200 and 400 mg/kg were administered by oral gavage FAV-100, FAV-200 and FAV-400 groups, respectively. Then, in the HG group, only distilled water (0.5 mL) was given in the same way. This procedure was repeated twice a day for one week. At the end of this period, the rats were euthanised with a high dose (50 mg/kg) of thiopental sodium anaesthesia and lung tissues were removed. Lung tissue samples were stored at -80°C until the time of analysis. The MDA, tGSH, SOD, TOS, TAS and OSI levels were measured in the excised lung tissues. The tissues were also examined histopathologically. The results obtained from all groups were evaluated by comparing between groups.

Preparation of samples: First, a 50 mM (pH = 7.2) buffer mixture was prepared with potassium phosphate monobasic and potassium phosphate dibasic. Weighed lung tissues were quickly ground in a mortar by adding liquid nitrogen. Then, placed in Eppendorf tubes and kept in the refrigerator. Buffer mixture was added to each pipette the weight of each tissue and homogenates were prepared. Then all tissues were centrifuged at 4°C at 15000 rpm for 15 min and the supernatants were kept on hold at -80°C.

Biochemical analysis

MDA, tGSH, SOD and protein analysis: The MDA, GSH and SOD in tissue sections were analysed using commercially available animal "Enzyme-Linked Immunosorbent Assay" (ELISA) kits and each assay was performed in accordance with the kit instructions (CAT No: E0156Ra, EA0113Ra and E0168Ra, respectively, BT Lab Zhejiang, China ELISA). The Bradford method was used for protein determination by spectrophotometry at 595 nm[14].

TOS and TAS analysis: The TOS and TAS levels were measured to determine oxidative stress. The kits catalog numbers (E1512Ra and E1710Ra, respectively, BT Lab Zhejiang, China ELISA).

Oxidative stress index (OSI): The OSI findings were calculated and analyzed according to the formula[15]:

$$\frac{\text{TOS}}{\text{TAS}}\times 100$$

Histopathological analysis: Lung tissues were fixed in 10% neutral formalin at necropsy. Tissues were subjected to routine alcohol-xylene processing and embedded in paraffin blocks. As 4 µ sections were cut and stained with Haematoxylin and Eosin (H&E). Grading of the severity of the histopathological findings was 0-3 (0: Normal, 1: Mild, 2: Moderate and 3: Severe injury) regarding interstitial pneumonia and lymphoid hyperplasia. Histopathology was performed by a pathologist who was blinded to treatment and group allocations.

Statistical analysis: The IBM SPSS 22.0 (IBM Corp. Released 2013. Armonk, NY) and GraphPad Prism 8 were used for all statistics. For biochemical analysis, the Shapiro-Wilk test was used to determine whether the groups were normally distributed. Because histopathological data are ordinal data, the evaluation was made with the Kruskal Wallis test and stated as Median (quartile 1-3). For biochemical findings, one-way ANOVA test was used in the analysis because the data showed normal distribution and the number of groups was more than two. The Tukey's HSD test was the preferred test for the determination of differences between groups in further analysis. Biochemical results obtained from the experiments were expressed as "Mean±Standard Deviation" (x±SD). Also, $p<0.05$ was considered significant.

RESULTS

Biochemical results

MDA and tGSH analyses: As shown in Fig. 1a and Table 1, there was a significant increase in MDA levels in the lung tissues of the favipiravir (100-200-400 mg/kg) groups compared to the HG group ($p<0.001$) and (Fig. 1b) decrease in tGSH levels favipiravir (100-200-400 mg/kg) groups according to the HG group ($p<0.001$).

Table 1: Results of biochemical data in lung tissue

Variables	MDA (nmol/mL)	tGSH (mg/mL)	SOD (ng/mL)	TOS (U/mL)	TAS (U/mL)	OSI (arbitrary units)
Groups (X±SD)						
HG	2.93±0.26[a]	5.64±0.09[a]	6.92±0.13[a]	3.39±0.22[a]	9.26±0.20[a]	0.004±0.0002[a]
FAV-100	3.79±0.15[b]	4.64±0.19[b]	5.80±0.06[b]	4.40±0.17[b]	8.32±0.22[b]	0.005±0.0002[b]
FAV-200	4.75±0.15[c]	3.34±0.11[c]	4.69±0.12[c]	5.46±0.26[c]	7.57±0.17[c]	0.007±0.0004[c]
FAV-400	6.61±0.15[d]	2.06±0.15[d]	2.51±0.14[d]	7.17±0.47[d]	5.67±0.13[d]	0.126±0.0009[d]
95% CI						
HG						
Lower	2.65	5.54	6.79	3.16	9.05	0.003
Upper	3.21	5.74	7.06	3.62	9.47	0.003
FAV-100						
Lower	3.79	4.43	5.74	4.22	8.08	0.005
Upper	3.96	4.84	5.86	4.58	8.55	0.005
FAV-200						
Lower	4.59	3.22	4.56	5.19	7.39	0.006
Upper	4.90	3.45	4.81	5.73	7.75	0.007
FAV-400						
Lower	6.44	1.90	2.36	6.68	5.53	0.011
Upper	6.77	2.23	2.66	7.66	5.80	0.013
p-values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
F-value						
df (3,23)	423.81	687.44	1599.73	172.65	410.60	318.60

[a,b,c,d]$p<0.001$ compared to other groups, HG: Healthy group, FAV-100: Favipiravir 100 mg/kg, FAV-200: Favipiravir 200 mg/kg, FAV-400: Favipiravir 400 mg/kg, MDA: Malondialdehyde, tGSH: Total Glutathione, SOD: Superoxide dismutase, TOS: Total oxidant status, TAS: Total antioxidant status, OSI: Oxidative stress index, CI: Confidence interval and X: Mean, SD: Standard deviation. After ANOVA test, Tukey's HSD was performed as *post hoc* (N = 6)

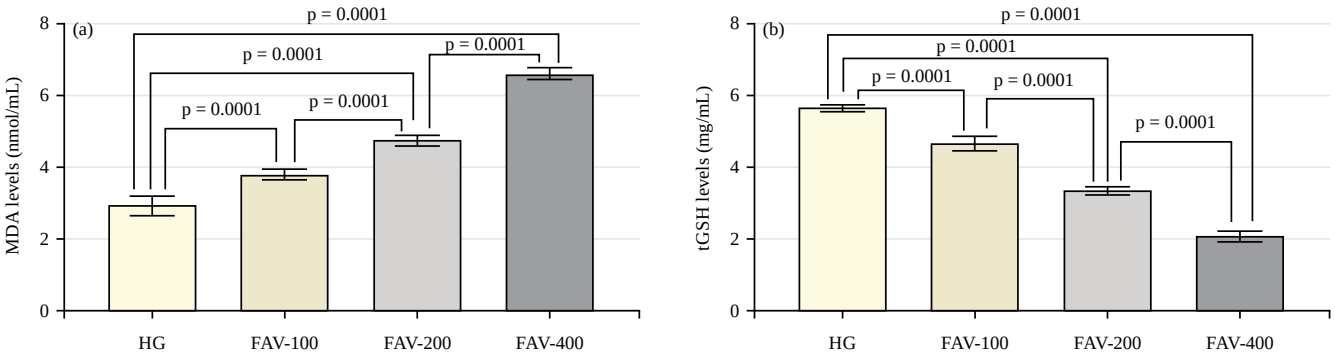

Fig. 1(a-b): MDA and tGSH levels in the lung tissue of experimental groups

MDA: Malondialdehyde, tGSH: Total glutathione, HG: Healthy, FAV-100: 100 mg/kg favipiravir, FAV-200: 200 mg/kg favipiravir and FAV-400: 400 mg/kg favipiravir. All groups were compared among themselves

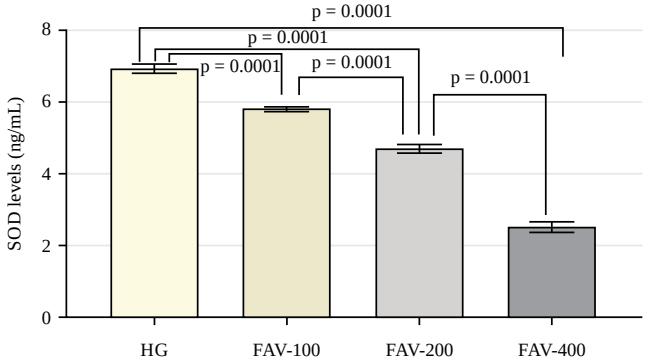

Fig. 2: SOD levels in the lung tissue of experimental groups

SOD: Superoxide dismutase, HG: Healthy, FAV-100: 100 mg/kg favipiravir, FAV-200: 200 mg/kg favipiravir and FAV-400: 400 mg/kg favipiravir. All groups were compared among themselves

Table 2: Statistical analysis of histopathological data obtained from the groups

Variables	Interstitial pneumonia	Lymphoid hyperplasia
Groups		
Median (quartile 1-3)		
HG	0 (0-0)[a]	0 (0-0)[a]
FAV-100	1 (0-1)[b]	1 (0-1)[b]
FAV-200	2 (1-2)[c]	2 (1-2)[c]
FAV-400	3 (2-3)[d]	3 (2.25-3)[d]
95% CI		
HG		
Lower bound	-	-
Upper bound	-	-
FAV-100		
Lower bound	0.51	0.55
Upper bound	0.98	1.05
FAV-200		
Lower bound	1.70	1.66
Upper bound	2.18	2.11
FAV-400		
Lower bound	2.56	2.60
Upper bound	2.87	2.89
p-values	<0.001	<0.001
H-values	113.77	113.36

[a,b,c,d]Groups identified by the same letter are statistically similar, but there is a statistically significant difference at the level of $p<0.05$ between groups identified by different characters. HG: Healthy, FAV-100: 100 mg/kg favipiravir, FAV-200: 200 mg/kg favipiravir and FAV-400: 400 mg/kg favipiravir and CI: Confidence interval (N = 6)

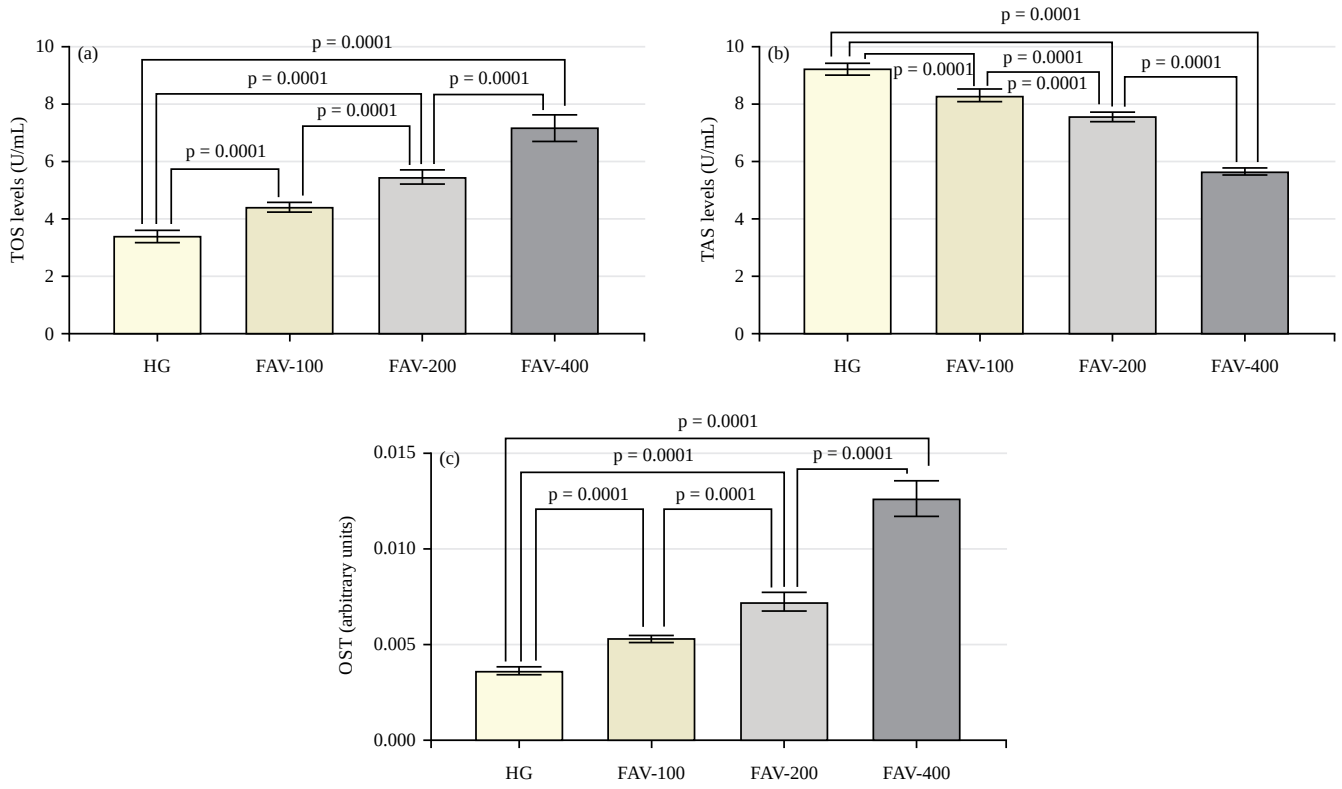

Fig. 3(a-c): TOS, TAS and OSI levels in the lung tissue of experimental groups

TOS: Total oxidant status, TAS: Total antioxidant status, OSI: Oxidative stress index, HG: Healthy, FAV-100: 100 mg/kg favipiravir, FAV-200: 200 mg/kg favipiravir and FAV-400: 400 mg/kg favipiravir. All groups were compared among themselves

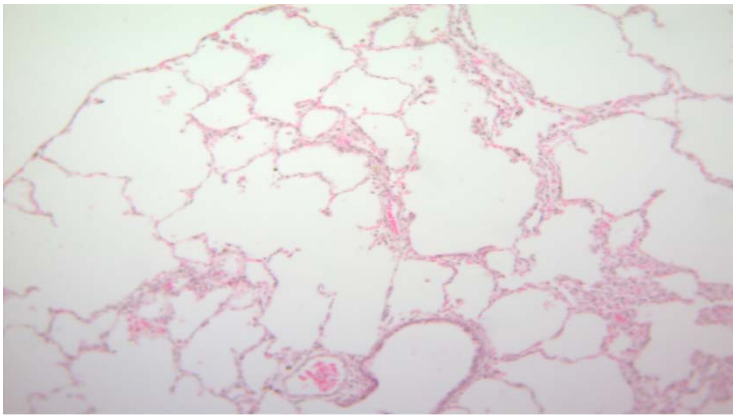

Fig. 4: Normal histological structure of lung tissue of healthy group

SOD analysis: The SOD activity was statistically significantly decreased in all favipiravir-treated groups according to the healthy group ($p<0.001$) as presented in Fig. 2c and Table 1.

TOS, TAS and OSI analysis: As indicated in Fig. 3a, TOS levels increased significantly in the groups receiving favipiravir at doses of 100, 200 and 400 mg/kg, TAS levels decreased significantly ($p<0.001$) compared to HG (Fig. 3b). The OSI levels increased significantly in the groups administering favipiravir at doses of 100, 200 and 400 mg/kg compared to HG ($p<0.001$) (Fig. 3c, Table 1).

Histopathological findings: As seen in Fig. 4, histopathological evaluations of lung tissue from the healthy group showed a normal appearance.

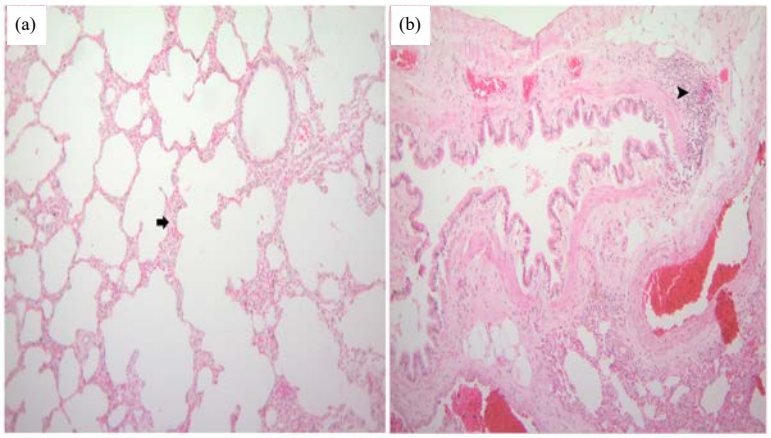

Fig. 5(a-b): Histopathological appearance in lung tissue of the 100 mg/kg favipiravir (FAV-100), (a) Arrow; mild interstitial pneumonia and (b) Arrowhead; lymphoid hyperplasia

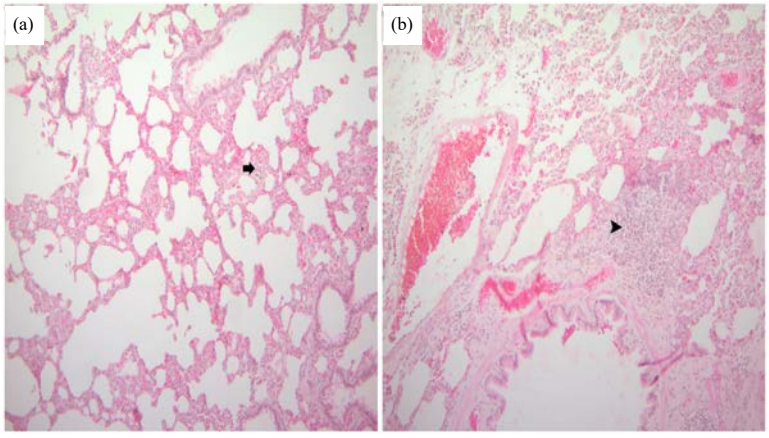

Fig. 6(a-b): Histopathological appearance in lung tissue of the 200 mg/kg favipiravir (FAV-200), (a) Arrow; moderate interstitial pneumonia and (b) Arrowhead; lymphoid hyperplasia

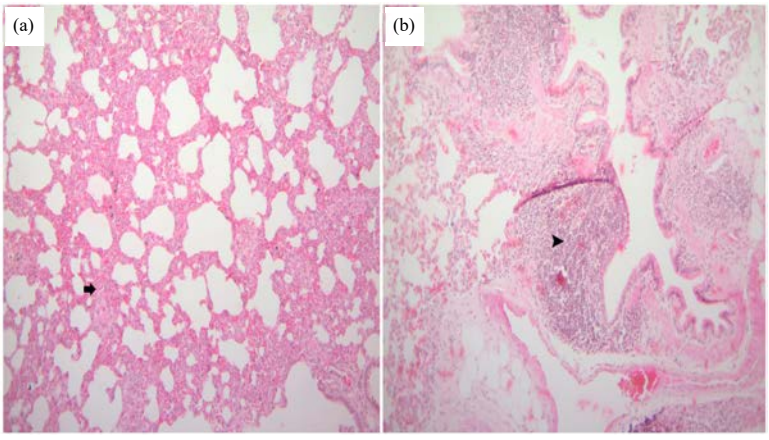

Fig. 7(a-b): Histopathological appearance in lung tissue of the 400 mg/kg favipiravir (FAV-400), (a) Arrow; severe interstitial pneumonia and (b) Arrowhead; lymphoid hyperplasia

Mild interstitial pneumonia (Fig. 5a) and lymphoid hyperplasia (arrowhead) (Fig. 5b) were observed in the lung tissue (arrow) of the FAV-100 group.

In the FAV-200 group, (arrow) moderate interstitial pneumonia (Fig. 6a) and (arrowhead) lymphoid hyperplasia (Fig. 6b) were seen.

Severe interstitial pneumonia (Fig. 7a) and (arrowhead) lymphoid hyperplasia (Fig. 7b) were observed in the FAV-400 group (Table 2).

DISCUSSION

From the experimental findings, favipiravir (100, 200 and 400 mg/kg) increased MDA and TOS levels and decreased tGSH, SOD and TAS levels. Changes in these parameters increased with increasing doses. With increasing doses of favipiravir, interstitial pneumonia and lymphoid hyperplasia in lung tissue are more severe. In recent years, serious side effects have been reported when high doses of favipiravir are administered[16,17]. With the recognition of these side effects, clinical studies on the efficacy, safety and dosage of favipiravir have recently intensified[18]. No studies were found in the literature on the toxic effects of favipiravir on the lung. This experimental study investigated and evaluated biochemically and histopathologically whether favipiravir has a toxic effect on the lungs.

In healthy tissues, oxidants and antioxidants are in balance. When this balance is altered in favour of the oxidants, oxidative damage occurs[19]. Malondialdehyde (MDA), an end product from lipid peroxidation (LPO), is also the strongest mutagen[20]. In the present study, there was a statistically significant increase in MDA in all favipiravir-treated groups, from normal levels in the lung tissue of the healthy group. Furthermore, this increase was observed to be favipiravir dose-dependent. In other words, MDA production increased in parallel with the rise in favipiravir dose. It is well known that MDA is a reliable oxidant parameter for the assessment of oxidative stress. Therefore, an increase in MDA levels in a tissue is an indication of an increase in ROS[21].

One of the most important antioxidants in the prevention of oxidative damage, the maintenance of redox and the regulation of its support is GSH. The amount of tGSH decreased in lung tissues with high MDA levels, as shown by our experimental results. Bilgin *et al.*[22] reported that tGSH decreased with increasing MDA levels in cytarabine-induced pulmonary edema and oxidative stress. In another study, favipiravir increased GSH-depleted oxidative stress in the heart and skin[11]. In the current study, tGSH levels in the lung tissue of people using favipiravir decreased in the normal period FAV-100 group of healthy groups. The level of this decreased significantly more at the 400 mg/kg dose of FAV than at the 200 mg/kg dose of FAV.

One of the antioxidant defense mechanisms evolved in living organisms against oxidative stress is SOD. In the present study, SOD levels in the lung tissue of animals given 100 mg/kg of favipiravir were significantly reduced compared to the healthy group. In other groups receiving favipiravir, SOD levels decreased with increasing doses. This was explained by increasing oxidative stress in animal liver tissue, causing a significant decrease in SOD levels[13]. Kara *et al.*[12] also reported that favipiravir caused inflammation in the kidney and liver tissue of the animals used and caused a significant decrease in SOD levels on days 10-15 of treatment. Total oxidative damage was determined by using TOS, TAS and OSI, which are markers of oxidative stress[23]. A study was conducted to investigate and compare the effects of favipiravir on rat ovarian tissue at doses of 100 and 400 mg/kg. The authors explained that favipiravir increased the TOS level in ovarian tissue at both doses compared to the healthy group. However, the TOS level increased more at the 400 mg/kg dose[10]. The TOS levels in lung tissue were normal in the healthy group and increased with favipiravir administration. For the doses of favipiravir, TOS levels in the lungs were evaluated as 400>200>100 mg/kg.

Another parameter that can determine the presence and severity of oxidative damage is the level of TAS. The experimental results showed a significant decrease in TAS as the dose of favipiravir was increased. Furthermore, the increase in oxidative parameters correlated with the decrease in TAS. Some reports are showing that both therapeutic and high doses of favipiravir increase oxidative damage in different tissues and organs[10-13]. Balcı *et al.*[10] administered favipiravir at low (100 mg/kg) and high (400 mg/kg) doses to rats. As a result of the experiment, there was an increase in TAS levels in rat ovarian tissue at both low and high doses.

It is well known that OSI is a parameter used to determine the best oxidant and antioxidant status, showing the relationship between oxidative stress and human health and disease[24]. As can be understood from our results, OSI was found to be high in the lung tissue of favipiravir-treated animals in which MDA and TOS levels were measured to be high. Our biochemical test results and information from the literature suggested that favipiravir is a dose-dependent inducer of oxidative damage in lung tissue.

In the present study, the biochemical findings were consistent with histopathology. Mild interstitial pneumonia and lymphoid hyperplasia were seen in lung tissue at the 100 mg/kg dose of favipiravir. Depending on the dose, interstitial pneumonitis and lymphoid hyperplasia in the lung tissue were moderate at 200 mg/kg and severe at the high dose of 400 mg/kg. It is well known that pneumonia is usually a polyetiological inflammation of the lungs[25]. It is found that no reports of favipiravir-induced interstitial pneumonia in literature. There are known cases reporting the development of interstitial pneumonia with clopidogrel[26]. In a further study, class III antiarrhythmics and EGFR inhibitors have been associated with interstitial pneumonia[27]. The literature reported that bronchoalveolar lavage fluid from a patient with drug-associated pneumonia contained abundant inflammatory cells[27]. In a study in agreement with the biochemical and histopathological findings, ROS-induced oxidative stress may be one of the causal factors in the development of interstitial pneumonia[28].

Infections involving lung tissue come to the fore when considering the indications for favipiravir[29]. It is certainly possible that the pulmonary toxic effects of favipiravir may overshadow its therapeutic benefits. Our study results show that favipiravir causes pulmonary toxicity that increases with dose and that oxidative processes play a role in the pathogenesis of toxicity. Therefore, our study may provide a basis for preclinical and clinical testing of drugs able to prevent favipiravir-induced oxidative damage.

CONCLUSION

The use of favipiravir in high doses of COVID-19 brought with it many side effects. Studies have been continuing in this direction in recent years. The lung toxicity of favipiravir, both at high doses and at different doses, has not been investigated before. For this reason, the study results were evaluated both biochemically and histopathologically. According to these results, favipiravir caused oxidative damage by significantly increasing MDA and TOS levels and decreasing tGSH, SOD and TAS levels in rat lung tissue at doses of 100, 200 and 400 mg/kg. When favipiravir was administered in increasing doses, it was easier to observe the changes between the different groups. These findings are also in line with the histopathological data. Interstitial pneumonia and lymphoid hyperplasia developed and worsened in the lungs of the rats as the dose of favipiravir increased.

SIGNIFICANCE STATEMENT

In this research, favipiravir administered to rats at increasing doses (100, 200 and 400 mg/kg) was found to cause biochemical and histopathological damage in the lungs. Favipiravir caused oxidative damage in lung tissue by inhibiting the increase in MDA and TOS levels and the suppression of tGSH, SOD and TAS levels. Interstitial pneumonia and lymphoid hyperplasia developed and worsened in the lungs of the rats as the dose of favipiravir increased. This study is the first to investigate the dose-dependent lung toxicity of favipiravir. The study recommendation is that dose adjustment in the clinical use of favipiravir has an important role in terms of lung toxicity. The dose of favipiravir that would cause fewer side effects in humans needs further study.

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