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Research Article

Pharmacokinetic Interaction of Favipiravir with Citalopram and Pioglitazone

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ABSTRACT

The current study's objective was to investigate the interactions of favipiravir with pioglitazone and citalopram. 25 Spraque-Dawley female rats were used in the study. Rats in groups 1 and 4 were given pioglitazone (1 mg/kg/day) for 7 days and rats in groups 2 and 5 were given citalopram (1.5 mg/kg/day) for 7 days. Rats in groups 3, 4, and 5 were given a loading dose (50 mg/kg) on the 6th day of the study and a maintenance dose of favipiravir (30 mg/kg) on the 7th day of the study. After the last drug administration, blood samples were taken from the rats at 15, 30, and 45 minutes, and 1, 2, 4, 6, and 8 hours. Plasma concentrations of drugs were determined by high-performance liquid chromatography (HPLC). The aldehyde oxidase (AO) and xanthine oxidase (XO) activities in liver tissues were determined by enzyme-linked immunosorbent assay (ELISA). Pioglitazone changed the pharmacokinetics of favipiravir and increased $t_{1/2}$, AUC, MRT and Cl values. Favipiravir did not affect the pharmacokinetics of pioglitazone at a steady state. When used together, favipiravir significantly decreased Cl while increasing citalopram's $t_{1/2}$, AUC, and MRT values. While citalopram increased the $t_{1/2}$, C_{max}, AUMC, and Cl values of favipiravir, it decreasing the AUC value. Pharmacokinetic drug interactions have been determined between favipiravir and AO substrates or modulators. It is thought that if the results obtained are supported by human studies, it will guide the concomitant use of these drugs in the clinic to prevent the occurrence of adverse reactions.

Keywords: Drug-drug interaction; Favipiravir; Pioglitazone; Citalopram; Aldehyde oxidase

INTRODUCTION

Favipiravir was first approved for the treatment of pandemic influenza in Japan in 2014.[1] In addition, it is widely used in the treatment of COVID-19, as it has been proven to be effective against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which emerged in Wuhan, China in 2019.[2] It has a broad spectrum of activity against RNA viruses, including rhinovirus and respiratory syncytial virus, apart from SARS-CoV-2 and influenza virus.[3–5] Its acts selectively and potently inhibits RNA-dependent RNA polymerase (RdRP).[6]

Favipiravir is administered orally and is metabolized in the liver mainly by aldehyde oxidase (AO) and partially by xanthine oxidase (XO). Metabolites are excreted from the body through the kidneys.[7,8] Since favipiravir inhibits the AO enzyme responsible for its metabolism, an oral loading dose is required at first administration to achieve adequate blood levels.[9]

Citalopram, a selective serotonin reuptake inhibitor (SSRI), is widely used in the treatment of depression and anxiety. It reaches stable blood concentration in plasma after one week of regular use and AO plays a role in its metabolism together with cytochrome P450 enzymes.[10,11]

Pioglitazone is used in the treatment of type 2 diabetes. As an agonist of peroxisome proliferator-activated receptor gamma (PPAR-γ) enhances insulin sensitivity.[12] Pioglitazone is metabolized by cytochrome P450 enzymes.[13] Pioglitazone inhibits the AO enzyme.[14]

Since citalopram and pioglitazone are drugs that require long-term use, oral administration of favipiravir may be necessary for treatment in people who contract COVID-19

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while using these drugs. Because favipiravir is metabolized by AO and also inhibits this enzyme, drug-drug interactions may occur when co-administered with AO substrates or modulators. However, the pharmacokinetic interaction of favipiravir with citalopram and pioglitazone is unknown.

Evaluation of data from pharmacokinetic studies will help to understand the drug-drug interaction mechanisms between favipiravir, citalopram, and pioglitazone. Based on results from pharmacokinetic studies, appropriate dosing regimens are facilitated, and side effects avoided.

In this study, it was aimed to investigate the drug-drug interaction between favipiravir, citalopram and pioglitazone. It is thought that the results obtained will guide the prevention of adverse drug reactions that may occur with the simultaneous use of these drugs in the clinic.

MATERIALS AND M ETHODS

Chemicals

Xanthine oxidase (E1263Ra) and aldehyde oxidase (ER0670) ELISA kits were purchased from FineTest Bioassay Technology Laboratory. Methanol, ethyl acetate, and other chemicals used in the study were obtained from Sigma-Aldrich.

Animals

The Institutional Animal Use and Care Committee of Firat University established rules for the humane treatment of all animals, and the same committee also approved the experiment's protocol (Ethical Approval Number: 2021/02). 25 female Sprague Dawley rats (12 weeks, 250-300 g) were obtained from the Laboratory of Experimental Animals of Firat University. The animals were provided with a standard pellet diet and ad libitum water. Rats were randomly divided into five experimental groups with five animals in each group. Group 1: Pioglitazone, Group 2: Citalopram, Group 3: Favipiravir, Group 4: Favipiravir+Pioglitazone, Group 5: Favipiravir+Citalopram.

Experimental protocol and blood sampling

Pioglitazone (Glifix tablet, Bilim İlaç Sanayii ve Ticaret A.Ş, Turkey) was dissolved in water and administered daily for 7 days by oral gavage at a dose of 1 mg/kg. Citalopram (Citol tablet, Abdi İbrahim İlaç Sanayii ve Ticaret A.Ş, Turkey) was dissolved in water and administered daily for 7 days by oral gavage at a dose of 1.5 mg/kg. Favipiravir (FAVIRA tablet, Novelfarma İlaç San. Ve Tic. Ltd. Şti., Turkey) was dissolved in 0.5% carboxymethyl cellulose (CMC) and administered to the rats by gavage at a loading dose of 50 mg/kg on the 6th day of the study, and a maintenance dose of 30 mg/kg was given on the 7th day. On the 7th day of the study, blood samples were collected at 0, 15, 30, and 45 min and 1, 2, 4, 6, and 8 h after ketamine (5 mg/kg)–xylazine (40 mg/kg) administration. Samples were collected into tubes containing EDTA from jugular veins (approximately 0.2 mL of blood was drawn each time) and were separated to sera by centrifugation at 4 °C for 30 min at 3.500 xg. After the end of the experiment; rats were sacrificed according to animal use guidelines. Liver tissues were obtained from decapitated animals at the end of the study. Tissues and plasma samples taken were stored in a deep freezer at -80 °C until analysis.

Analytical Procedure

Preparation of stock solutions

The stock solutions for favipiravir and citalopram were prepared in methanol at a concentration of 300 μg/mL. The stock solution for pioglitazone was prepared in dimethyl sulfoxide (DMSO) at a concentration of 100 μg/mL.

Determination of favipiravir level

Plasma was dissolved at +4 °C. 0.3 mL of methanol was added to 0.2 mL of plasma. The mixture was centrifuged at 4000 xg for 5 minutes. A 20 μl of the supernatant was injected directly into the HPLC-UV device carrying the C18 column (4 μm particle size, 150 x 4.6 mm i.d., Genesis, Leicestershire, UK). Chromatography conditions were adjusted according to the method suggested by Bulduk.[15]

Determination of citalopram level

Plasma was dissolved at +4 °C. 0.15 mL of methanol was added to 0.1 mL of plasma. The mixture was vortexed and centrifuged at 4000 xg for 5 minutes. 40 μl of the supernatant was injected directly into the HPLC-UV device carrying the C18 column (5 μm particle size, 250 x 4.6 mm i.d., Inertsil ODS-3, GL Sciences, Torrance, CA, USA) Chromatography conditions were adjusted according to the method suggested by Rodríguez et al.[16]

Determination of pioglitazone level

Plasma was dissolved at +4 °C. 0.05 ml of 0.1 mol/L potassium di-hydrogen phosphate (K_2HPO_4) was added to 0.2 mL of plasma and the mixture was vortexed. Then, 1 mL of ethyl acetate was added to the mixture and vortexed for 3 minutes. After the samples were centrifuged at 1300 xg for 6 minutes, the upper phase was transferred to another tube and dried in a 45 °C water bath under nitrogen gas. After the obtained supernatant was dried under nitrogen gas, the residue was dissolved in 0.2 mL DMSO and 40 μl of the solution was injected into the HPLC-UV device carrying the C18 column (4 μm particle size, 150 x 4.6 mm i.d. Genesis Leicestershire, UK). Chromatography conditions were adjusted according to the method suggested by Saha et al.[17]

Pharmacokinetic analysis

Chromatographic images obtained by injecting drugs into the high-performance liquid chromatography (HPLC-UV) (Shimadzu, Tokyo, Japan) device was calculated according to 6-point calibration curves prepared with different concentrations of standard solutions for each drug. The HPLC system consists of a pump (LC-20AT controlled by CBM-20A), an auto-sampler (SIL-20A), a degasser (DGU-20A), a column oven (CTO-20A), and a UV-VIS (SPD- 20A) consisted of the detector. Pharmacokinetic parameters were determined using a PKSolver add-in, in Microsoft Excel, per methods described in Zhang et al.[18] Non-Compartmental Analysis was employed to calculate pharmacokinetic Parameters.

Elimination half-life ($t_{1/2}$), the area under the plasma-concentration-time curve (AUC), area under the initial plasma concentration-time curve (AUMC), mean residence time (MRT), clearance (Cl), and apparent volume of distribution (V_d) were determined. Maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were determined using a direct plasma concentration-time curve.

Determination of aldehyde oxidase and xanthine oxidase activity

Rats were sacrificed, and liver tissues were removed. Before homogenization, tissues were weighed and thoroughly washed in ice-cold phosphate-buffered saline (PBS) (pH 7.4). The needed number of tissues were extracted, and they were then homogenized in PBS using a glass homogenizer on ice (tissue weight (g): PBS (mL) volume=1:9). The supernatant was then obtained by centrifuging the homogenates at 5000 x g for 5 minutes. Using commercially available kits (ER0670, E1263Ra; Fine Test, Bioassay Technology Laboratory, and BT Lab, respectively), liver tissue concentrations of AO and XO were measured in accordance with the manufacturer's recommendations. For AO and XO, the values were measured in ng/mL.

Statistical analyses

With the help of the IBM SPSS 22.0 package application, descriptive analysis done(SPSS Inc., Chicago, IL, United States). Descriptive statistics of the data are presented as Mean±SD. The Levene test and the Shapiro-Wilk test were used to test the homogeneity of variance and the assumption of normality, respectively. Mann-Whitney U test was used to compare pharmacokinetic parameters. The statistical analysis of enzyme activity was performed using one-way analysis of variance (ANOVA) and the post hoc Tukey HSD test, $p<0.05$ was considered statistically significant.

An arbitrary effect size of 0.25 (=0.05) was used to assess the statistical power of the sample size. The power was 0.998 with the sample size that was provided. The software G*Power 3.1 was used to calculate power.

RESULTS

Method validation

Standard calibration lines subjected to linear regression analysis produced a range of Regression coefficient (R) values between 0.9986 and 0.9999. The lowest recovery value of the methods was determined as 85%. Chromatograms of favipiravir, pioglitazone, and citalopram concentrations in plasma are presented in Figure 1. The retention times for the favipiravir, pioglitazone and citalopram were 5.5, 7.5, and 8.5 min, respectively.

Aldehyde Oxidase and Xanthine Oxidase Activities in Liver Tissue

There was no significant difference in liver aldehyde oxidase (AO) enzyme activities between the groups in which pioglitazone and favipiravir were administered alone ($p>0.05$). However, when favipiravir and pioglitazone were administered together, AO enzyme activity was found to be statistically significantly decreased ($p<0.008$, Figure 2A). The xanthine oxidase (XO) enzyme activity was not significant difference between the favipiravir group and the favipiravir+pioglitazone group ($p>0.05$), but XO in these groups wassignificantly lower than the pioglitazone group ($p<0.008$, Figure 2B).

There was no significant difference in liver AO activity in the citalopram group and the favipiravir group ($p>0.05$), but the AO activity of the citalopram group was found to besignificantly higher than the favipiravir+citalopram group ($p<0.008$, Fig.2C). Liver XO enzyme activity was found to be significantly lower in the groups in which favipiravir was administered alone or in combination with citalopram compared to the group in which citalopram was administered alone ($p<0.008$, Figure 2D). There was no significant difference in XO activities in the groups in which favipiravir was administered alone and together with citalopram ($p>0.05$, Figure 2D).

Pharmacokinetic Parameters

Effect of favipiravir on pioglitazone pharmacokinetics

The plasma concentration-time curve following oral administration of pioglitazone alone and in combination with favipiravir is presented in Figure 3A and Table 1. It was observed that administration of favipiravir did not affect the T_{max}, AUC, and Cl of pioglitazone. No statistically significant difference was observed in pharmacokinetic parameters between pioglitazone and favipiravir+pioglitazone groups ($p>0.05$).

Effect of pioglitazone on favipiravir pharmacokinetics

The plasma concentration-time curve following oral administration of favipiravir alone and in combination with pioglitazone is presented in Figure 3 B and Table 1. When

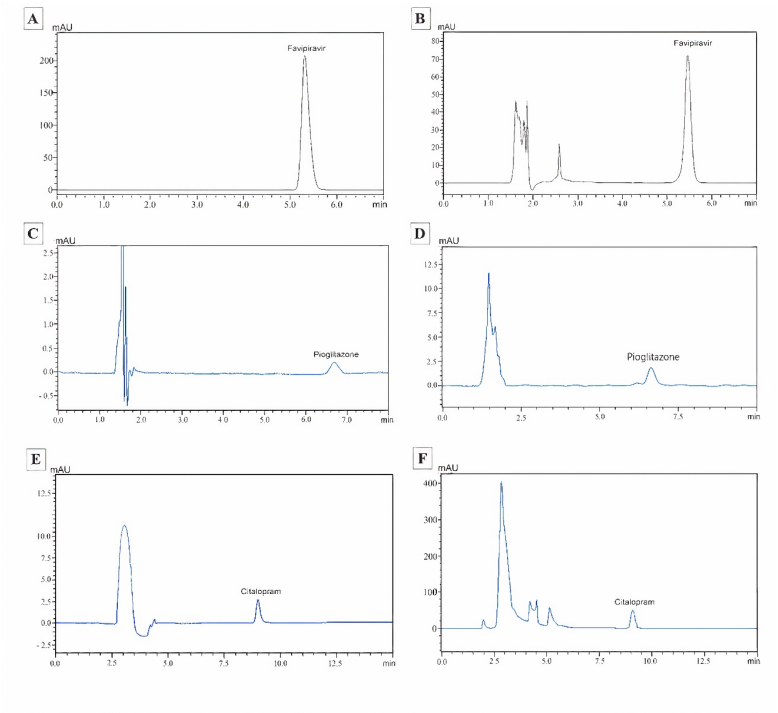

Fig. 1: Chromatograms of favipiravir, pioglitazone, and citalopram analysis in standard solution and plasma [A: Favipiravir standard, B: Favipiravir 6th hour plasma; C: Pioglitazone standard, D: Pioglitazone 4th hour plasma; E: Citalopram standard, F: Citalopram 2nd hour plasma]

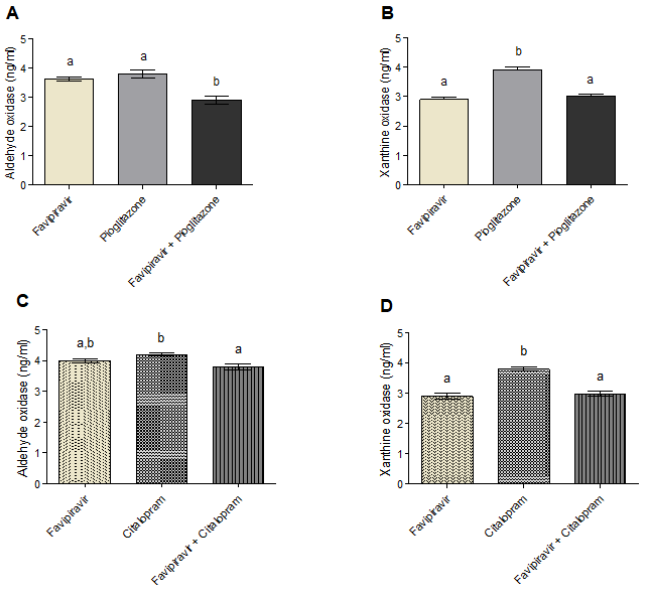

Fig. 2: Liver AO and XO enzyme activities after oral administration of favipiravir, citalopram, and pioglitazone to rats [A: AO activity in groups treated with favipiravir and pioglitazone, B: XO activity in groups treated with favipiravir and pioglitazone, C: AO activity in groups treated with favipiravir and citalopram, D: XO activity in groups treated with favipiravir and citalopram]. a and b represent statistical differences between groups ($p< 0.05$)

compared with the favipiravir group, the elimination $t_{1/2}$, AUC, AUMC, MRT, Vd ($p<0.008$), and Cl ($p<0.004$) values were found to be statistically significantly increased in the favipiravir+pioglitazone group.

Effect of favipiravir on citalopram pharmacokinetics

The plasma concentration-time curve following oral administration of citalopram alone and in combination with favipiravir is presented in Figure 4 A and Table 2. It was determined that the administration of favipiravir caused changes in some pharmacokinetic parameters of citalopram. While $t_{1/2}$, AUC, and MRT increased ($p<0.008$)significantly in the favipiravir+citalopram group compared to the citalopram group alone; it was determined that AUMC and Cl values decreased ($p<0.008$).

Effect of citalopram on favipiravir pharmacokinetics

The plasma concentration-time curve following oral administration of favipiravir alone and in combination with citalopram is presented in Figure 4B and Table 2. $t_{1/2}$, C_{max}, AUMC, MRT, and Cl values were found to be statistically significantly increased ($p<0.008$)in the favipiravir+citalopram group compared to the group treated with favipiravir alone. AUC and Vd parameters were found to be significantly decreased ($p<0.008$).

DISCUSSION

Orally administered favipiravir is metabolized in the liver mainly by AO and partially XO enzymes.[7,8] The AO enzyme metabolizes favipiravir and is also inhibited by favipiravir.[7] Therefore, drug-drug interactions become inevitable when favipiravir is co-administered with AO substrates or modulators. Citalopram is a drug used to treat depression and anxiety. In addition to cytochrome P450 enzymes, the AO enzyme also takes part in the metabolism of Citalopram.[11] It has been reported that pioglitazone, which is used in the treatment of type-2 diabetes, is an AO enzyme inhibitör.[12,14] Drug interactions are not known when favipiravir is co-administered with citalopram and pioglitazone. Therefore, in the current study, the possible drug interaction between favipiravir when used together with citalopram and pioglitazone was investigated.

Pioglitazone is mainly metabolized by CYP2C8, CYP3A4, and CYP2C9 enzymes.[19] Pioglitazone is an inhibitor of CYP2C8 and CYP3A4 in in vitro studies. However, it has not been reported to inhibit or induce CYP enzymes in in vivo studies.[19] In an in vitro study, it was found that pioglitazone inhibited the AO enzyme.[14] Therefore, the potential for drug interactions is increased when pioglitazone is co-administered with favipiravir.

There was a significant decrease in liver AO enzyme activities in the favipiravir + pioglitazone group compared to the groups treated with favipiravir and pioglitazone alone. However, AO enzyme activities were found to be similar in groups treated with favipiravir and pioglitazone alone. Our study results show that pioglitazone, like favipiravir, inhibits AO and inhibition is higher when both are used together (Figure 2A).[14] Possible interaction of pioglitazone with other drugs has been studied, but significant pharmacokinetic interactions have not been identified.[13,20] In the current study, we found that $t_{1/2}$, AUC, AUMC, MRT, Vd and Cl pharmacokinetic values of favipiravir were significantly increased when used with pioglitazone (Table 1). This difference in favipiravir pharmacokinetics is likely due to AO enzyme inhibition by pioglitazone (Figure 2 A).[14] As a result of inhibition of the AO enzyme by pioglitazone, we found that the biological half-life and residence time of favipiravir were prolonged, and its plasma concentration increased.

In addition, we found that there was no significant difference in XO enzyme activities between the favipiravir+pioglitazone group and the favipiravir group, but these two groups had lower XO enzyme activities than the pioglitazone group (Figure 2B). Based on these results, it can be saidthat favipiravir partially occupies the enzyme as it is an XO substrate, as described in previous studies, whereas pioglitazone does not affect XO.[7,19,21]

Clopidogrel inhibits pioglitazone metabolism and gemfibrozil increases the plasma concentration of pioglitazone. Itraconazole does not have a significant effect on the pharmacokinetics of pioglitazone.[22,23] Clopidogrel and gemfibrozil increase pioglitazone plasma concentration, possibly by inhibiting CYP2C8.[22,23] Similarly, in another study, it was reported that caffeine increased the C_{max}, T_{max}, AUC, and $t_{1/2}$ values of pioglitazone.[24] In the current study, it was found that favipiravir did not affect pioglitazone pharmacokinetics. This is because pioglitazone is metabolized by cytochrome p450 enzymes and probably because favipiravir has no inhibition or induction effect on these enzymes.[7,19]

Citalopram is metabolized by cytochrome P450 enzymes[10] and partially by AO enzyme.[11] Therefore, drug interactions may occur between favipiravir, which is both metabolized by AO and inhibits this enzyme, and citalopram. It has been reported that fluconazole, a CYP450 enzyme inhibitor, when used together with citalopram, changes the pharmacokinetics of citalopram.[25] In another study, cannabidiol was found to inhibit the CYP450-mediated metabolism of citalopram.[26]

There has been an AO enzyme-related interaction between citalopram and favipiravir (Figure 2C).Since favipiravir is highly metabolized by AO, the simultaneous administration of citalopram, which is metabolized by AO, results in decreased metabolism by partially occupying the substrate-binding sites of the enzyme, reducing its association the enzyme.[7,11] Thus, the plasma concentration of favipiravir increased, and the time to stay in the body and the time to be eliminated from the body were prolonged (Table 2). In addition, as a result of inhibition of the

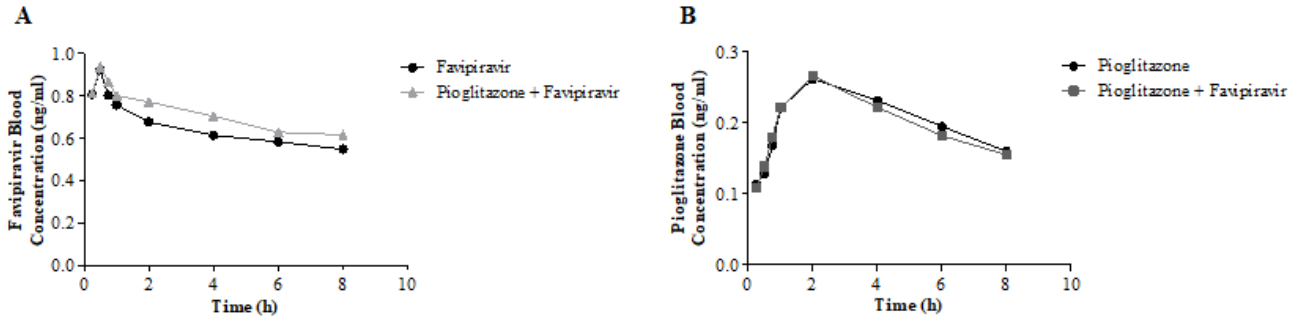

Fig. 3: Plasma concentration-time curve of drugs after single and co-administration of favipiravir and pioglitazone [A: Plasma concentration-time curve of favipiravir, B: Plasma concentration-time curve of pioglitazone]

Table 1: Pharmacokinetic parameters of the two drugs in plasma following administration of favipiravir and pioglitazone alone or combination inrats (n=5)

Parameters	Favipiravir	Favipiravir+Pioglitazone (Favipiravir)	Pioglitazone	Favipiravir+Pioglitazone (Pioglitazone)
$t_{1/2}$(h)	16.17±0.18	17.14±0.54[a]	7.46±0.18	7.62±0.50
T_{max} (h)	0.50	0.50	2.00±0.01	2.00±0.02
C_{max} (μg/mL)	921.75±0.43	936.0±20.03	0.26±0.01	0.27±0.03
AUC 0-t (μg/mL*h)	5146.31±1.84	5589.88±36.74[a]	164.76±4.5	160.75±5.13
AUMC (h^2*μg/mL)	423483.5±68.9	519976.26±384.59[a]	387.77±10.39	385.70±9.41
MRT (h)	23.47±0.25	24.97±0.65[a]	11.51±1.16	11.65±0.47
Vd (L/kg)	0.039±0.0009	0.0970±0.0110[a]	0.26±0.05	0.27±0.01
Cl (mL/h/kg)	0.0017±0.0001	0.0039±0.0003[a]	0.02	0.02

C_{max}: maximum plasma concentration reached, T_{max}: time to reach C_{max}, $t_{1/2}$=:elimination half-life, AUC: Area under the plasma concentration-time curve, AUMC: Area under the initial plasma concentration-time curve, MRT: Mean residence time, Vd: Volume of distribution at steady-state, Cl: clearance. [a]; $p<0.05$ represents the statistical difference in the pharmacokinetic parameters of favipiravir when administered alone and in combination with pioglitazone.

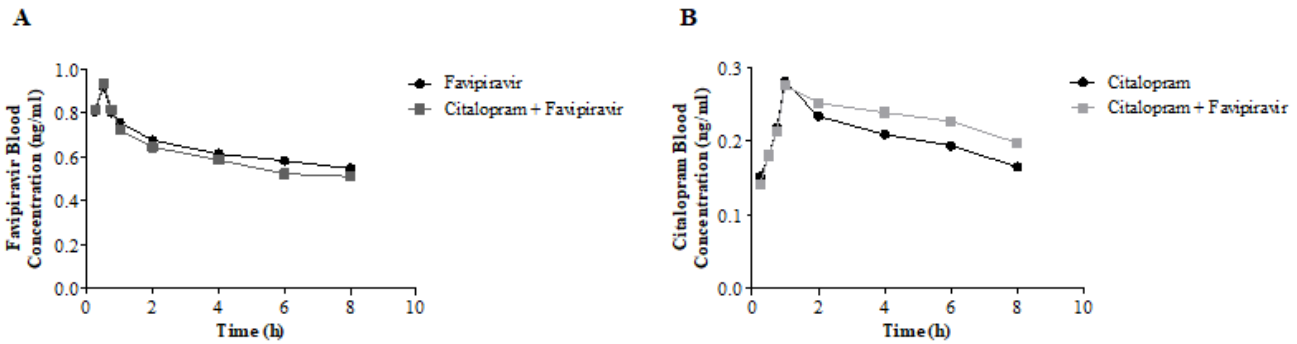

Fig. 4: Plasma concentration-time curve of drugs after single and co-administration of favipiravir and citalopram [A: Plasma concentration-time curve of favipiravir, B: Plasma concentration-time curve of pioglitazone]

Table 2: Pharmacokinetics of two drugs in plasma following administration of favipiravir and citalopram alone or combination in rats (n=5)

Parameters	Favipiravir	Favipiravir+Citalopram (Favipiravir)	Citalopram	Favipiravir+Citalopram (Citalopram)
$t_{1/2}$(h)	16.17±0.18	17.03±0.34[a]	12.35±0.48	16.28±0.21[b]
T_{max} (h)	0.50	0.50	1.00	1.00±0.01
C_{max} (μg/mL)	921.75±0.43	932.0±0.90[a]	0.28±0.01	0.28±0.05
AUC 0-t (μg/mL*h)	5146.31±1.84	4791.88±230.53[a]	163.51±9.51	181.00±22.68[b]
AUMC (h^2*μg/mL)	423483.5±68.9	426618.10±146.16[a]	821.58±12.09	155.78±2.19[b]
MRT (h)	23.47±0.25	24.59±0.18[a]	17.96±0.49	23.95±0.80[b]
Vd (L/kg)	0.039±0.0009	0.011±0.0061[a]	0.32	0.30±0.04
Cl (mL/h/kg)	0.0017±0.0001	0.0047±0.0011[a]	0.018	0.012[b]

C_{max}= maximum plasma concentration reached, T_{max}= time to reach C_{max}, $t_{1/2}$= elimination half-life, AUC= Area under the plasma concentration-time curve, AUMC= Area under the initial plasma concentration-time curve, MRT= Mean residence time, Vd= Volume of distribution at steady-state, Cl= clearance.
[a]; p<0.05 represents the statistical difference in the pharmacokinetic parameters of favipiravir when administered alone and in combination with citalopram.
[b]; p<0.05 represents the statistical difference in the pharmacokinetic parameters of citalopram when administered alone and in combination with favipiravir.

AO enzyme by favipiravir, plasma residence time and the time taken for elimination from the body were prolonged for citalopram, which is partially metabolized by AO. The pharmacokinetic results and the data obtained from the liver AO enzyme activity support the study stating that although citalopram is mainly metabolized by CYP450 enzymes, the AO enzyme also has an important place in its metabolism. [11]

CONCLUSION

Favipiravir may interact with pioglitazone and citalopram at the AO and XO enzyme level. As a result, the pharmacokinetics of these drugs may change. Therefore, concomitant use of favipiravir with pioglitazone and citalopram may increase the effects of these drugs and the risk of dose-related side effects.If the results obtained from this study are supported by human studies, it is thought that the concomitant use of these drugs in the clinic will be a guide in preventing the occurrence of adverse reactions.

AUTHORS' CONTRIBUTIONS

Idea/Concept: Zeliha KESKİN ALKAÇ, Dilan AŞKIN ÖZEK, Songül ÜNÜVAR; Design:Zeliha KESKİN ALKAÇ, Dilan AŞKIN ÖZEK, Neşe BAŞAK TÜRKMEN; Data Collection and/or Processing: Zeliha KESKİN ALKAÇ, Dilan AŞKIN ÖZEK, Hande YÜCE, Fatih Ahmet KORKAK, Neşe BAŞAK TÜRKMEN, Sümeyye ASLAN; Analysis and/or Interpretation: Zeliha KESKİN ALKAÇ, Hande YÜCE, Fatih Ahmet KORKAK, Neşe BAŞAK TÜRKMEN; Literature Review: Zeliha KESKİN ALKAÇ; Writing the Article: Zeliha KESKİN ALKAÇ; Critical Review: Songül ÜNÜVAR, Dilan AŞKIN ÖZEK.

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Conflict to interest

The authors report there are no competing interests to declare.

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