THE IRAQI JOURNAL OF
VETERINARY MEDICINE
eISSN:2410-7409
pISSN: 1609-5693

OPEN ACCESS

Pharmacokinetic Interaction Between Favipiravir and Amlodipine in Hypertensive Local Rabbits (*Oryctolagus cuniculus*)

Ali I Al-ameedi[1*], Falah M AL-Rekabi[2]

[1]Department of Physiology and Pharmacology, College of Veterinary Medicine, Al-Qasim Green University, Babylon, Iraq, [2]Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq

***Correspondence:**
ali.alameedi@vet.uoqasim.edu.iq

Received: 11 January 2023
Revised: 27 January 2023
Accepted: 19 February 2023
Published: 28 Jun 2023

DOI:
https://doi.org/10.30539/ijvm.v47i1.1499

Cite:
Al-ameedi AI, AL-Rekabi FM. Pharmacokinetic interaction between favipiravir and amlodipine in hypertensive local rabbits (*Oryctolagus cuniculus*). Iraqi J. Vet. Med. 2023;47(1):38-43.

ABSTRACT

In the treatment of COVID-19, the antiviral medication Favipiravir has proven to be quite successful. Its metabolism is mediated by the enzymes aldehyde oxidase (AO) and xanthine oxidase (XO). This research investigated the potential drug-drug interaction between favipiravir and amlodipine in hypertensive rabbits. Twenty local adult male rabbits (aged between 10 and 12 months and weighing between 2 and 2.5 kg) were induced with hypertension by 20 mg/kg BW of desoxycorticosterone acetate subcutaneously for three weeks and then divided randomly into two groups of ten. The first group received a single oral dose of 40 mg/kg BW of favipiravir, while the second group received 5 mg/kg of amlodipine orally for 14 consecutive days to inhibit AO before receiving a single oral dose of 40 mg/kg BW of favipiravir. Blood samples were collected from the marginal ear vein at 15, 30, 45 min, and 1, 2, 4, 8, 12, 24, 48, 36, 48, and 72 h. High-performance liquid chromatography (HPLC) was used to determine the concentration of favipiravir in the plasma. The results showed that co-administration of amlodipine prolonged the time taken for favipiravir (T_{max}) to reach maximum plasma concentration (C_{max}) and decreased its elimination half-life, while increasing the area under the curve (AUC). Amlodipine also prolonged the elimination of favipiravir by reducing the clearance per unit time (Cl/f). Additionally, hypertension potentiated the effect of amlodipine on the absorption, distribution, metabolism, and excretion of favipiravir. In conclusion, concomitant use of favipiravir with other drugs that affect AO enzyme activity may alter the pharmacokinetic profile of the drug. Therefore, adjusting the dose of favipiravir administered to hypertensive patients receiving amlodipine is recommended.

Keywords: favipiravir, amlodipine, pharmacokinetics, aldehyde oxidase, hypertension

INTRODUCTION

Drug-drug interactions (DDIs) are the most common cause of concern to patients receiving combination therapy. The World Health Organization underlines that adverse drug reactions and their consequences can be considerably reduced by paying close attention to the population at risk of DDIs (1). Favipiravir is a novel antiviral medication that inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses in a highly specific and effective manner. (2). It is activated phosphorylated in cells and identified as a substrate by viral RNA polymerase, limiting RNA polymerase function. As a result, it was speculated that favipiravir would have a powerful antiviral impact on SARS-CoV2, an RNA virus (3). Favipiravir has an oral bioavailability of higher than 95%. Favipiravir is mostly metabolized by aldehyde oxidase (AO). In humans, the plasma half-life is around 4 h (4). Cytochrome P450

Isoenzymes do not play any role in the metabolic process of favipiravir (5). Therefore, the pharmacokinetic profiles of favipiravir may shift when it is concomitantly used with other drugs that modify the AO enzyme activity. A major contributor to cardiovascular mortality, hypertension is a global epidemic. The majority of hypertension individuals need to take medicine to keep their blood pressure in the normal range, and of those, over 70% need to take two or more antihypertensive medications simultaneously (6). Because of their age, concomitant illnesses, polypharmacy, and lengthy hospital stay, hypertensive patients are more prone to DDIs (7). Amlodipine is a calcium channel blocker antihypertensive agent that acts as an arterial vasodilator that lowers blood pressure by relaxing vascular smooth muscle (8). Multiple medication administration is obligatory in the treatment of COVID-19, particularly in patients with fundamental illnesses (hypertension, diabetes, and cardiovascular diseases) (9). Drug-drug interactions are a subject that has to be addressed in clinical practice. There is currently little information available on DDI induced by favipiravir (10). Therefore, in this study, drug interaction at the pharmacokinetic and enzyme activity was investigated between favipiravir, which is used successfully in the treatment of COVID-19, with amlodipine in hypertensive rabbits.

MATERIALS AND METHODS

Ethics

All procedures used in this experiment were reviewed and approved in accordance with animal welfare ethical standards by the Scientific Committee of the Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Baghdad and the local Committee for Animal Care and Use at the College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq.

Experimental Animals

Twenty healthy adult male local rabbits (*Oryctolagus cuniculus*), aged between 10 and 12 months and weighing between 2-2.5 kg, were acquired from Iraqi local farms in Baghdad. The rabbits were housed in stainless-steel cages in a temperature-controlled setting ranging from 20 to 25 °C with humidity maintained at 50±5% and a 12-hour light/dark cycle to reduce anxiety. Before starting the experiment, the animals were held for at least two weeks to allow for adaptation. The experiments were carried out in the animal house of Veterinary Medicine College, University of Baghdad.

Induction of Hypertension

The twenty rabbits were divided randomly into two equal groups. Subcutaneous injections of 20 mg/kg desoxycorticosterone acetate (DOCA, Dechra® Europe) were given to the rabbits twice weekly for three weeks to induce hypertension. The rabbits were then given 1% NaCl solution instead of water for consumption (11). One week following the start of the trial, the blood pressure of the experimental animals was measured using a rabbit blood pressure cuff (Vetronic Services LTD, UK) with an electronic monitor (Medaval, China). The blood pressure was recorded within normal limits using a power lab instrument.

Experimental Design

The study aimed to investigate the pharmacokinetic profile of favipiravir in hypertensive rabbits after a single oral administration. The first group (hyFav) consisted of 10 rabbits induced with hypertension by 20 mg/kg of DOCA subcutaneously for three weeks and then received a single oral dose of 40 mg/kg BW/rabbit of favipiravir. The second group (hyFav+Am) also consisted of 10 rabbits induced with hypertension by 20 mg/kg of DOCA subcutaneously for three weeks. However, they received 5 mg/kg of amlodipine orally for 14 consecutive days to inhibit AO before receiving a single oral dose of 40 mg/kg BW/rabbit of favipiravir.

Blood Sampling

Blood samples (1 mL) were obtained from the ear marginal vein by cannulation technique (cannula gage 27) from each animal using a plastic syringe of 3 mL. Samples were collected at 15, 30, 45 min, and 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 h. The plasma was separated from the blood by using anticoagulant EDTA test tubes and centrifuging the samples for 10 min at 3000 rpm before transferring the plasma to a 1 mL Eppendorf tube. The tubes were dated, timestamped, and stored in a freezer at -20 °C until analysis could be done (12). Plasma samples were diluted to the required concentration (µg/mL) before analyzing the concentration of favipiravir using HPLC.

Preparation of Stock Solutions

The recommended human doses of favipiravir (Awamedica® Pharmaceutical Company, Iraq) and amlodipine (Actavis® UK), respectively, are 200 mg and 10 mg per tablet. In order to convert the human dose to an animal dose, the equation provided by Nair and Jacob (2016) (13) was used, which calculates the animal equivalent dose (AED) using the following formula:

$$\text{AED (mg/kg)} = \text{Human dose (mg/kg)} \times K_m \text{ ratio}$$

Where K_m ratio is the correction factor and calculated for rabbits as 3.1. To prepare the amlodipine solution, the tablets were crushed and dissolved in 20 mL of sterile distilled water to achieve a concentration of 0.5 mg/mL. The oral dose was then prepared at 0.5 mg/kg BW and administered orally at a rate of 1 mL/kg BW using a stomach tube. To prepare the favipiravir solution, the tablets were crushed and dissolved in 10 mL of sterile distilled water to achieve a concentration of 20 mg/mL. The

effective dose of favipiravir is 800 mg/person per day, which corresponds to an oral dose of 40 mg/kg BW. This dose was administered as a single dose via stomach tube at a rate of 2 mL/kg BW.

Determination of Favipiravir Concentration

To determine the concentration of favipiravir in plasma, 0.2 mL of plasma was thawed at 4 °C and mixed with 0.3 mL of methanol (99.9% Sigma® USA). The mixture was then centrifuged at 4000 rpm for 5 min, and a supernatant volume of 20 µL was injected directly into the High-performance liquid chromatography (HPLC) column. Chromatography conditions were adjusted according to the method described by Bulduk (14).

Pharmacokinetic Analysis

The drugs were injected into an HPLC (Shimadzu, Tokyo, Japan, serial No: L215056), and chromatographic curves were generated using 6-point calibration curves generated with various concentrations of standard solutions. Pharmacokinetic parameters were computed using PK-Solver, a non-compartmental analysis pharmacokinetics software tool (15).

Calibration Curve of Favipiravir

To generate calibration curves, six distinct favipiravir standard solutions were prepared with concentrations ranging from 5-30 µg/mL. Three separate injections of each standard solution were made into the HPLC machine under optimal chromatographic conditions (columns at a constant temperature of 30 °C and a flow rate of 1.5 mL/min). Sample and standard injection volumes were 100 µL, and the peak area was quantified at 360 nm using the Waters 2996 Photodiode Array Detector. The linear equation of the generated calibration curve was as follows: y = 81995x + 448.3, R^2 = 0.9999 [y = peak area, x = concentration (µg/mL)]. The recovery was more than 98% based on repeated studies (n=5) at low, medium, and high concentrations within the calibration range. Samples were analyzed for favipiravir (n=10), with a limit of detection (LOD) of 0.9 µg/mL and a limit of quantification (LOQ) of 2.7 µg/mL.

Statistical Analysis

To determine the influence of various factors on research parameters, the Statistical Analysis System (SAS) program was used. The t-test was performed to compare means, and the chi-square test was performed to compare percentages at $P \leq 0.05$. Correlation coefficient estimation was used to analyze the variables in this research (16).

RESULTS

Induction of Hypertension

The result of the current study revealed there were significant increases ($P<0.05$) in systolic and diastolic blood pressure in all experimental rabbits after induction comparing with those before three weeks of DOCA administration (Tablet 1 and Figure 1). The blood pressure remained higher than the normal value.

Table 1. Mean blood pressure (mmHg) of experimental rabbits before and after induce hypertension within three weeks

	Group		
Blood pressure	**hyFav**	**hyFav+Am**	**LSD**
Systolic before induction	130.0±0.966 ^{Ab}	129.0±1.789 ^{Ab}	4.360
Systolic after induction	162.5±1.285 ^{Aa}	160.8±1.579 ^{Aa}	3.813
Diastolic before induction	80.83±1.302 ^{Ab}	81.50±1.232 ^{Ab}	3.053
Diastolic after induction	95.67 ± 1.256 ^{Aa}	95.67±1.145 ^{Aa}	3.220

Values are mean±SEM, n=10. $^{A-B}$Values with different uppercase superscripts are statistically significant ($P \leq 0.05$) between groups. $^{a-b}$Values with different lowercase superscript are significantly different ($P \leq 0.05$) within a group. hyFav: Rabbits induced with hypertension using 20 mg/kg of desoxycorticosterone acetate (DOCA) and treated with a single oral dose of 40 mg/kg BW/rabbit of favipiravir. hyFav+Am: Rabbits induced with hypertension using 20 mg/kg of DOCA, treated withC 5 mg/kg of amlodipine to inhibit aldehyde oxidase (AO), and then treated with a single oral dose of 40 mg/kg BW/rabbit of favipiravi

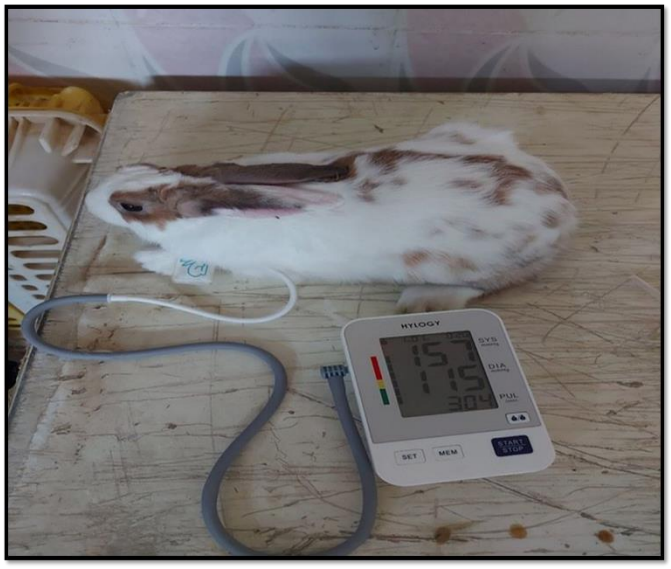

Figure 1. The measurement of blood pressure in a rabbit using a HYLOGY digital blood pressure monitor. The monitor displays readings for systolic blood pressure ("SYS"), diastolic blood pressure ("DIA"), and heart pulse ("PUL")

Chromatographic Analysis

Favipiravir was detected in the sample, with sharp, well-defined peaks under the chromatographic conditions that were applied. The retention time of the favipiravir was found to be 4.87±0.18 min and the retention time of the internal standard was 5.00±0.07 min. The method developed was validated for Linearity, LOD and LOQ, specificity, Dilution of Integrity, and Recovery (Figure 2).

Calibration Curve Linearity

The calibration function (peak area ratio vs Concentration) was linear over a working range of 25-200 µg/mL. with six points of calibration used for quantification by linear regression. The regression equation for the analysis was y = 0.8024x – 10.069 with a coefficient of correction (R^2) = 0.9999 (Figure 2).

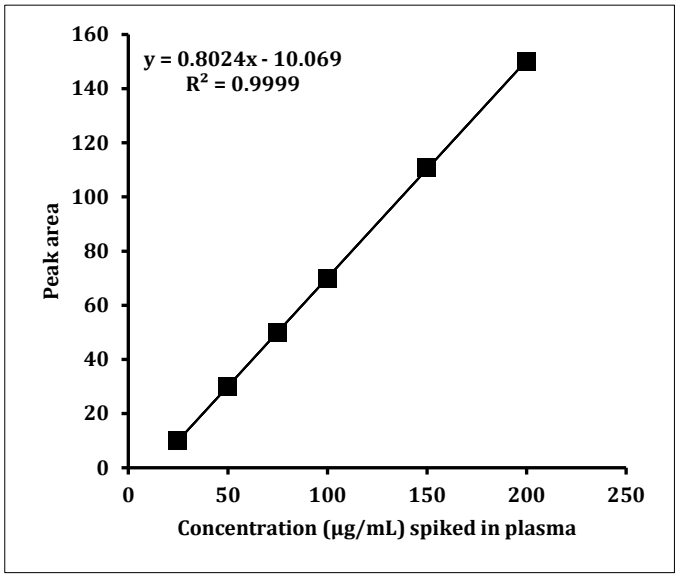

Figure 2. Calibration curve of favipiravir in plasma as a standard

Pharmacokinetic of Favipiravir

The plasma concentration of favipiravir versus the time curve in rabbits after a single oral 40 mg/kg BW administration of favipiravir is shown in Table 2 and Figure 3. It appeared that favipiravir was quickly absorbed, as evidenced by the peak concentration (C_{max}) of 14.77±0.075 µg/mL and 13.42±0.034 µg/mL in the hypertensive rabbits treated with amlodipine (hyFav+Am) and without amlodipine (hyFav), respectively. The plasma favipiravir concentration versus time data was best fitted to a biexponential equation corresponding to a two-compartmental open model. The absorption of the drug was clearly evidenced by the observed absorption rate constant ($t_{1/2ka}$) and elimination half-life of the absorption phase ($t_{1/2a}$). The hypertensive rabbits treated with amlodipine (hyFav+Am) showed a longer elimination half-life of the elimination phase ($t_{1/2e}$) and absorption rate constant (5.84±0.018 h and 5.41±0.021 h, respectively) compared with the rabbits without amlodipine (hyFav). Furthermore, the results revealed that the rabbits without amlodipine (hyFav) showed a higher apparent volume of distribution (Vd) which was 2.04±0.067 L. Additionally, the higher area under the curve (AUC 0-inf) appeared in the rabbits treated with amlodipine (hyFav+Am) (655.08±2.75 µg/mL*h). Finally, the inhibition of the AO enzyme by amlodipine in hypertensive rabbits strongly affected the clearance (CL) of favipiravir. The results of HPLC analysis demonstrated that the rabbits without amlodipine (hyFav) had insignificantly (P<0.05) higher clearance (0.088 L/h) than those treated with amlodipine (hyFav+Am).

Table 2. Pharmacokinetics parameters of single oral administration of 40 mg/kg BW favipiravir in hypertensive rabbits with and without amlodipine

Parameters	Groups		P-value t-test
	hyFav	hyFav+Am	
$t_{1/2}$a (h)	2.92±0.009	5.84±0.018	0.086*
$t_{1/2}$e (h)	16.61±0.003	37.40±0.085	0.036*
$t_{1/2}$ka (h)	2.62±0.002	5.41±0.021	0.041*
CL/F (L/kg/h)	0.088±0.002	0.060±0.003	0.022*
T_{max} (h)	8.09±0.001	11.79±0.013	0.038*
C_{max} (µg/mL)	13.42±0.034	14.77±0.075	0.152
AUC 0-inf (µg/mL*h)	450.27±1.041	655.08±2.75	0.045*
Vd (L)	2.04±0.067	1.17±0.078	0.098
F (%)	0.99±0.067	0.98±0.09	0.069
CL (L/h)	0.088±0.042	0.061±0.093	0.067*

$t_{1/2a}$: Elimination half-life of the absorption phase, $t_{1/2e}$: Elimination half-life of the elimination phase, $t_{1/2ka}$: Absorption half-life, CL/F: Apparent clearance, T_{max}: Time to reach maximum plasma concentration, C_{max}: Maximum plasma concentration, AUC 0-inf: Area under the plasma concentration-time curve from time zero to infinity, Vd: Volume of distribution, F: Bioavailability, CL: Clearance

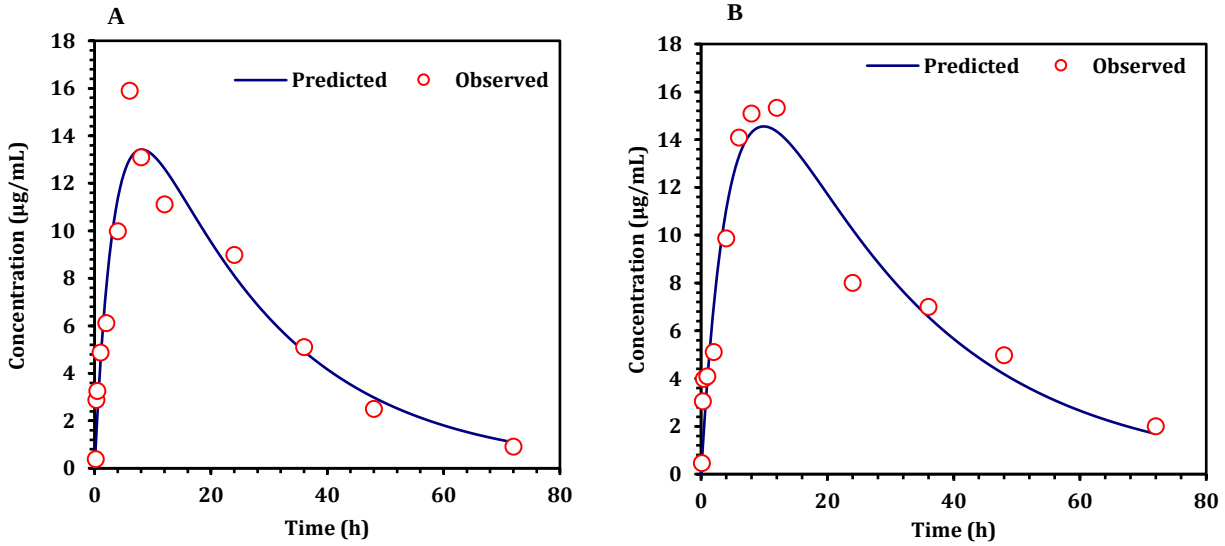

Figure 3. Concentration of favipiravir versus time. **(A)** hyFav (hypertensive without amlodipine). **(B)** HyFav+Am (hypertensive with amlodipine

DISCUSSION

Multiple medicines are often used in the treatment of COVID-19 in patients with chronic conditions such as hypertension, diabetes, and cardiovascular disease, as well as consequences such as acute respiratory distress syndrome, shock, arrhythmia, and acute renal damage (21). Unfortunately, there is a lack of information on the drug interactions that may be induced by favipiravir. In the liver, favipiravir is metabolized by AO found in the cytosol, but not by cytochrome 450. There is currently a lack of published evidence indicating whether or not favipiravir and its active metabolite, T-705-RTP, alter the activity of hepatic enzymes responsible for drug metabolism.

The retention of salt and water is induced by mineralocorticoid acting like aldosterone. Salt-sensitive hypertension is induced in deoxycorticosterone acetate (DOCA)-treated mice by drinking salt water (17). It has been suggested that vasopressin plays a central role in DOCA–salt hypertension. (18). For the purposes of pharmacokinetic and pharmacodynamics research, DOCA-salt rodents are commonly used as an animal model of human secondary hypertension. (19). Hypertension produced by DOCA-salt is typified by end-stage organ destruction, leading to cardiac and renal failure (20).

In this study, the administration of DOCA-salt to rabbits led to increases in systolic and diastolic blood pressure, as consequence of this, the local cardiac and renal tissue levels of angiotensin-II and aldosterone increased, as well as oxidative stress. The present study has investigated the pharmacokinetics of favipiravir in healthy and hypertensive rabbits with and without amlodipine. To the best of our knowledge, this is the first study of favipiravir pharmacokinetic interaction with amlodipine in rabbits. Favipiravir undergoes substantial oxidative (AO) and to a lesser extent xenobiotic (XO) hepatic metabolism, with the inactive metabolite favipiravir-M1 (F-M1) being eliminated via the kidneys (22). Even though favipiravir inhibits one of CYP450 components (CYP2C8) (23). Because of this, the investigation focused solely on the possible medication interactions with AO favipiravir. It is hypothesized that co-administration of favipiravir with an AO inhibitor, such as amlodipine, will reduce favipiravir clearance, leading to elevated plasma concentrations of favipiravir and lower M1 concentrations. However, there are no published trials looking at how the plasma concentration of favipiravir changes when an AO inhibitor is used at the same time (24). As a result of AO, pharmacological interactions may occur, and this fact should not be disregarded in clinical settings (25). Favipiravir and amlodipine were concomitantly administered to hypertensive rabbits to investigate any potential interactions. The relationship between AO activities and favipiravir metabolites (F-M1) was studied in the cytosol of the liver from 16 healthy adults (8 men, 8 women). The rate of F-M1 production was correlated with the strength of AO. F-M1 production was found to be decreased by 73.6%, 52.6%, and 27.3% by menadione, isovanillin, and allopurinol, respectively, in an in vitro investigation utilizing human hepatic cytosol. (26). These results show that favipiravir is less affected by XO inhibition and is metabolized by AO, which is consistent with the current study.

According to the current study, administering favipiravir with an AO inhibitor lowered favipiravir's metabolic clearance, resulting in higher favipiravir plasma concentrations. Favipiravir plasma concentrations enhanced the irreversible suppression of AO. This inhibition caused a faster increase in plasma favipiravir levels than before (without amlodipine). In the current study, the goal of using amlodipine was to inhibit aldehyde oxidase, not for the treatment of hypertension, so we don't evaluate the systolic and diastolic blood pressure after administration of amlodipine. Based on these findings, it might be concluded that the AO inhibitor has little effect on plasma favipiravir levels in rabbits with modest AO activity. Likewise, it is reasonable to assume that the effectiveness of medications used to block AO declines as their concentrations in the blood diminish (26). Demir et al. suggested that favipiravir may inhibit methotrexate elimination by inhibiting aldehyde oxidase (27). Interestingly, we determined that the pharmacokinetic parameters Cl, t1/2, and C_{max} all dropped while AUC values increased when favipiravir was co-administered with amlodipine. It is possible that Amlodipine has an effect on enzyme activities is responsible for its negative impact on favipiravir's clearance, C_{max}, and $t_{1/2}$ values. In an animal investigation, it was discovered that the AO activity of favipiravir was lower in female mice than in males. (26). There may be species, race, and sex differences in favipiravir metabolism and enzyme activities (28). The results of this study may have been affected by the dose administered, the difference between species, and the fact that there was a significant effect of hypertension on pharmacokinetic parameters.

ACKNOWLEDGEMENTS

The college of veterinary medicine at the University of Baghdad is highly appreciated by the authors for helping to accomplish this work. The authors are also extremely grateful to Dr. Wael Alsoufi and Dr. Laith Sadik from Veterinary Directorate, Department of biology and medical supervision, Baghdad in recognition of his work setting up the chromatographic condition.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Subramanian A, Adhimoolam M, Kannan S. Study of drug-Drug interactions among the hypertensive patients in a tertiary care teaching hospital. Perspect Clin Res. 2018;9(1):9-14.

2. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci 2017;93(7):449-63.
3. Hamza RZ, Al-Talhi T, Gobouri AA, Alsanie WF, El-Megharbel SM. Are favipiravir and acyclovir with IgG injections supplemented with vitamin D "suggested therapeutic option" can fight against COVID-19. Adv. Anim. Vet. Sci. 2021;9(4):549-554.
4. Singh TU, Parida S, Lingaraju MC, Kesavan M, Kumar D, Singh RK. Drug repurposing approach to fight COVID-19. Pharmacol Rep. 2020;72(6):1479-1508.
5. Kumar D, Trivedi N. Disease-drug and drug-drug interaction in COVID-19: Risk and assessment. Biomed Pharmacother. 2021;139:111642.
6. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-520.
7. Sivva D, Mateti UV, Neerati VM, Thiruthopu NS, Martha S. Assessment of drug-drug interactions in hypertensive patients at a superspeciality hospital. Avicenna J Med. 2015;5(02):29-35.
8. Shirley M, McCormack PL. Perindopril/amlodipine (Prestalia®): a review in hypertension. Am J Cardio Dru. 2015;15(5):363-370.
9. Rodriguez F, Solomon N, de Lemos JA, Das SR, Morrow DA, Bradley SM, et al. Racial and ethnic differences in presentation and outcomes for patients hospitalized with COVID-19: findings from the American Heart Association's COVID-19 Cardiovascular Disease Registry. Circulation. 2021;143(24):2332-2342.
10. Negru PA, Radu AF, Vesa CM, Behl T, Abdel-Daim MM, Nechifor AC, et al. Therapeutic dilemmas in addressing SARS-CoV-2 infection: Favipiravir versus Remdesivir. Biomed Pharmacother. 2022;147:112700.
11. Ahmad RM, Ibrahim OM. Effect of erythromycin on pharmacokinetics of Amlodipine in hypertensive rabbits. On. J Vet Res. 2019;23(6):555-567.
12. Harahap Y, Diptasaadya R, Purwanto DJ. Volumetric Absorptive Microsampling as a Sampling Alternative in Clinical Trials and Therapeutic Drug Monitoring During the COVID-19 Pandemic: A Review. Drug Des Devel Ther. 2020;14:5757-5771.
13. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm. 2016;7(2):27-31.
14. Bulduk İ. Comparison of HPLC and UV Spectrophotometric Methods for Quantification of Favipiravir in Pharmaceutical Formulations. Iran J Pharm Res. 2021;20(3):57-65.
15. Zhang Y, Huo M, Zhou J, Xie S. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Comput Methods Programs Biomed. 2010;99(3):306-314.
16. SAS S. User's guide: statistics. SAS Institute Inc, Cary, NC. 1985;956.
17. Delyani JA, Rocha R, Cook CS, Tobert DS, Levin S, Roniker B, et al. Eplerenone: a selective aldosterone receptor antagonist (SARA). Cardiovasc Drug Rev. 2001;19(3):185-200.
18. Yemane H, Busauskas M, Burris SK, Knuepfer MM. Neurohumoral mechanisms in deoxycorticosterone acetate (DOCA)–salt hypertension in rats. Exp Physiol. 2010;95(1):51-55.
19. Yang S, Lee YS, Oh E. Pharmacokinetics of drugs in spontaneously or secondary hypertensive rats. Xenobiotica. 2014;44(1):77-88.
20. Wang D, Luo Y, Myakala K, Orlicky DJ, Dobrinskikh E, Wang X, et al. Serelaxin improves cardiac and renal function in DOCA-salt hypertensive rats. Sci Rep. 2017;7(1):9793.
21. Yan H, Valdes AM, Vijay A, Wang S, Liang L, Yang S, et al. Role of drugs used for chronic disease management on susceptibility and severity of COVID-19: a large case-control study. Clin Pharmacol Ther.2020;108(6):1185-1194.
22. Özek DA, Keskin Z, Hande Y, Türkmen NB, Aslan S, Ünüvar S. Drug-drug interaction of aldehyde oxidase inhibitor and xanthine oxidase inhibitor with favipiravir. Value Health Sci. 2022;12(3):511-519.
23. Deb S, Arrighi S. Potential effects of COVID-19 on cytochrome P450-mediated drug metabolism and disposition in infected patients. Eur J Drug Metab Pharmacokinet. 2021;46(2):185-203.
24. Madelain V, Nguyen TH, Olivo A, De Lamballerie X, Guedj J, Taburet AM, et al. Ebola virus infection: review of the pharmacokinetic and pharmacodynamic properties of drugs considered for testing in human efficacy trials. Clin Pharmacokinet. 2016;55(8):907-923.
25. Du YX, Chen XP. Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. Clin Pharmacol Ther. 2020;108(2):242-247.
26. Mishima E, Anzai N, Miyazaki M, Abe T. Uric acid elevation by favipiravir, an antiviral drug. Tohoku J Exp Med. 2020;251(2):87-90.
27. Demir E, Sütcüoğlu O, Demir B, Ünsal O, Yazıcı O. A possible interaction between favipiravir and methotrexate: Drug-induced hepatotoxicity in a patient with osteosarcoma. J Oncol Pharm Pract. 2022;28(2):445-448.
28. Hanioka N, Saito K, Isobe T, Ohkawara S, Jinno H, Tanaka-Kagawa T. Favipiravir biotransformation in liver cytosol: Species and sex differences in humans, monkeys, rats, and mice. Biopharm Drug Dispos. 2021;42(5):218-225.

التداخل في الحركية الدوائية بين الفافيبيرافير والاملودبين في الارانب المحلية (*Oryctolagus cuniculus*) المصابة بارتفاع ضغط الدم

علي ابراهيم العميدي[1] ، فلاح موسى كاظم الركابي[2]

[1]فرع الفسلجة والادوية، كلية الطب البيطري، جامعة القاسم الخضراء، بابل، العراق، [2]فرع الفسلجة والكيمياء الحياتية والادوية، كلية الطب البيطري، جامعة بغداد، بغداد، العراق

الخلاصة

أثبت الدواء المضاد للفيروسات favipiravir فعاليه عالية في علاج حالات الكوفيد-١٩ . الألدهيد أوكسيديز (AO) وأكسيداز الزانثين(XO) هما الإنزيمات المسؤولة عن ايض العقار. بينت الدراسة في إمكانية حدوث تفاعلات دوائية بين عقاري الفافيبيرافير والأملوديبين في الأرانب المصابة بارتفاع ضغط الدمز تم تقسيم ٢٠ أرنبًا ذكرًا بالغًا محليًا (تتراوح أعمارهم بين ١٠ و ١٢ شهرًا ويزنون بين ٢ و ٢,٥ كجم) إلى مجموعتين عشوائيتين من عشرة أرانب لكل منهما. تلقت المجموعة الأولى جرعة فموية واحدة من ٤٠ ملغ/كجم من الفافيبيرافير، بينما تلقت المجموعة الثانية ٥ ملغ/كجم من الأملوديبين عن طريق الفم لمدة ١٤ يومًا متتالية لتثبيط AO قبل تلقي جرعة واحدة فموية من ٤٠ ملغ/كجم من الفافيبيرافير. . تم جمع عينات الدم من الوريد الأذني عند ١٥ و٣٠ و٤٥ دقيقة و١ و٢ و٤ و٨ و١٢ و٢٤ و٤٨ و٣٦ و٤٨ و٧٢ ساعة. تم استخدام كروماتوجرافيا سائلة عالية الأداء (HPLC) لتحديد تركيز عقار الفافيبيرافير في البلازما. اظهرت النتائج ان عقار الاملودبين قد اطال الوقت الذي يستغرقه عقار الفافيبيرافير (T_{max}) للوصول إلى اعلى تركيز في الدم (C_{max}) ، تم تقليل الحد الأقصى لتركيز المصل ونصف عمر الإطراح ، وزادت المنطقة الواقعة تحت المنحنى (AUC). كما عمل الاملودبين على تقليل نسبة الطرح لكل وحدة زمنية (Cl / f) عند تناوله مع favipiravir. وبالتالي تقليل نسبة التخلص من عقار الفافيبيرافير .من ناحية أخرى ، فان ارتفاع ضغط الدم يعمل على زيادة تاثير الأملوديبين في التأثير على الامتصاص والتوزيع وايض وطرح عقار الفافيبيرافير. في الختام ، فإن الاستخدام المتزامن للفافيبيرافير مع الأدوية الأخرى التي تؤثر على إنزيم الالديهايد اوكسيديز قد يسبب تغيرات في خصائص الحركية الدوائية للفافيبيرافير. وعليه ينصح إعادة تعديل نظام جرعة الفافيبيرافير مرضى ارتفاع ضغط الدم الذين يتناولون ادوية تؤثر على انزيم الديهايد اوكسيديز.

الكلمات المفتاحية: فافيبيرافير، املودبين، الديهايد اوكسيديز، الارانب، التداخل الدوائي