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SHORT COMMUNICATION

Pharmacokinetic characterization of favipiravir in patients with COVID-19

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This prospective observational study describes the pharmacokinetic characteristics of favipiravir in adult patients hospitalized for mild to moderate COVID-19 with a positive RT-PCR test. Favipiravir was administered for 5 days, with a loading dose of 3200 mg and a maintenance dose of 1200 mg/day. Serial blood samples were collected on Day 2 and Day 4 of the therapy. Laboratory findings of the patients ($n = 21$) and in-hospital mortality were recorded. Favipiravir concentrations exhibited substantial variability and a significant decrease during the treatment of COVID-19. The median favipiravir trough concentration ($C_{0\text{-trough}}$) on Day 2 was 21.26 (interquartile range [IQR], 8.37–30.78) μg/mL, whereas it decreased significantly to 1.61 (IQR, 0.00–6.41) μg/mL on Day 4, the area under the concentration–time curve decreased by 68.5%. Day 2 $C_{0\text{-trough}}$ of female patients was higher than male patients. Our findings indicate that favipiravir concentrations show significant variability during the treatment of COVID-19 and therapeutic drug monitoring may be necessary to maintain targeted concentrations.

KEYWORDS
COVID, favipiravir, pharmacokinetics, therapeutic drug monitoring

The authors confirm that the Principal Investigators for this study is Prof. Filiz Onat, and that she had direct clinical responsibility for patients.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is caused by the SARS Coronavirus 2 (SARS-CoV-2).[1] More than 3.4 million deaths and 165 million confirmed cases have been identified worldwide as of May 2021.[2] There are currently several antiviral medications undergoing evaluation as possible treatments for SARS-CoV-2, but to date there are no agents with proven efficacy.

Favipiravir is an antiviral agent that selectively and potently inhibits **RNA-dependent RNA polymerase** of RNA viruses and has been approved in Japan for the treatment of recent and re-emerging pandemic influenza. Consequently, favipiravir has a well-established and well-characterized safety profile.[3–6] However; favipiravir has a highly complicated pharmacokinetic profile.[7] Its plasma concentration decreases in nonhuman primates[8] and also in patients receiving Ebola virus disease therapy.[9]

The pharmacokinetic complexities and conflicting data on efficacy of favipiravir in COVID-19 patients suggest that more studies are needed to understand the pharmacokinetic variables that influence the clinical outcome. Thus, the goal of this prospective observational study was to gain an understanding of the pharmacokinetic properties of favipiravir at doses that are commonly used for the treatment of COVID-19 patients.

What is already known about this subject

- Favipiravir has been shown to be effective against SARS-CoV-2 virus in *in vitro* and animal studies.
- Modelling studies indicate variability in favipiravir serum concentrations.
- Serum trough concentrations of favipiravir in most samples were lower than the lower limit of quantification in the critically ill COVID-19 patients.

What this study adds

- Favipiravir serum concentration decreases significantly in patients with mild to moderate COVID-19 disease.
- Gender may affect favipiravir pharmacokinetics.
- Dose adjustment may be needed for favipiravir treatment in COVID-19 patients and therapeutic drug monitoring may be helpful.

2 | METHODS

2.1 | Patients

This study included adult patients hospitalized at Marmara University Hospital, Istanbul, Turkey, for mild to moderate COVID-19 according to Siddiqi and Mehra[10] during the period September–November 2020. Eligible patients with COVID-19 confirmed with a positive RT-PCR test were included in the study. Inclusion criteria were: >18 years of age, no difficulty in swallowing pills, no previous history of favipiravir use and favipiravir first dose administration time between 8:00 a.m. and 11:00 a.m. (so as to enable blood sampling to end before 12 pm). Patients using drugs which can interfere with favipiravir pharmacokinetics (e.g., aminophylline, theophylline), with severe kidney or liver disease and admitted to the intensive care unit were excluded. Ethical approval for the study was obtained from the Marmara University Ethical Committee (09.2020.470). All patients were treated according to the Turkish Ministry of Health national guideline for COVID-19.[11] Biochemical and haematological parameters with clinical features of the patients were recorded on admission, the day before the start of favipiravir therapy (Day 0) and at the end of favipiravir therapy on Day 5 (Table 1).

2.2 | Administration of favipiravir tablets and collection of blood samples

Favipiravir tablets (FAVIMOL©, 200 mg/tablet, Turkey) were administered with a regimen of a loading dose of 3200 mg and a maintenance dose of 1200 mg (1600 mg b.i.d. on Day 1 and 600 mg b.i.d. on Days 2–5) according to the guideline.[11] Patients were administered favipiravir at 8–10 a.m. and 8–10 p.m. on an empty stomach, half an hour before or 2 hours after the meal. Oral ingestion of favipiravir was supervised so as to avoid drug non-compliance. Venous blood samples were collected on Days 2 and 4, just before (trough concentration, 0 h) and following favipiravir ingestion at 0.5 h, 1 h, 2 h, 3 h, 6 h and 12 h later.

2.3 | Measurement of favipiravir concentrations

Favipiravir serum concentrations were determined by a high-performance liquid chromatography-mass spectrometry method (Q Exactive Focus Orbitrap LC–MS/MS System, Thermo Fisher Scientific, Bremen, Germany) in the Third Public Health Laboratory Maltepe, Istanbul, Turkey. Serum samples were heated to 60°C for half an hour to inactivate the virus.[9] Serum samples (250 μL) were transferred to a secondary tube, and pyrazinamide (100 μL of 62.5 ppm, Cayman Chemical, Michigan, USA) was added as the internal standard, followed by formic acid (25 μL of 0.1%, Merck, Darmstadt, Germany), and methanol (Supelco, Merck, Darmstadt, Germany). Following vortex (2 min) and centrifugation (2940 *g* for 10 min), supernatants (5 μL) were directly injected into the liquid chromatographic system (Thermo Scientific Dionex UltiMate 3000 UHPLC, Bremen, Germany). The HPLC column (Thermo Scientific Accucor Phenyl-Hexyl column, California, USA) was used for chromatographic separation. The retention time for favipiravir was 1.78 minutes. Analytes were detected using an electrospray ionization

TABLE 1 Characteristics of the participants at admission

	Median or *n*	Range (IQR 25th or 75th percentiles) or %
Patients	21	100
Gender		
Male	13	61.9
Female	8	38.1
Age	58	48.5–76
Age, ≥65 years	8	38.1
Smoking status		
Current	2	9.5
Former	5	23.8
Never	14	66.7
Body mass index		
≤ 24.9	2	9.5
25.0–29.9	11	52.4
≥ 30.0	8	38.1
Chronic diseases	16	76.2
Cardiovascular disease	8	38.1
Hypertension	14	66.7
Chronic lung disease	3	14.3
Diabetes mellitus	4	19.0
Chronic kidney disease	2	9.5
Dyspnoea at admission	12	57.1
Hypoxia at admission	6	28.6
Laboratory findings		
Lymphocyte number	1100	900–1350
AST	32.0	29.0–44.0
ALT	19.0	15.0–33.0
LDH	316.0	243.0–371.0
BUN	14.0	10.5–20.5
Creatinine	0.78	0.63–0.96
Fibrinogen	426.0	345.5–544.5
D dimer	0.650	0.360–1.445

source in the negative ion mode. The precision of the method was 18%, bias was 4.25%, limit of detection (LOD) was 0.80 μg/mL and linearity was 0.80–100 μg/mL. The lowest limit of quantification (LOQ) for favipiravir was 1.0 μg/mL.

2.4 | Pharmacokinetic parameters

Serum concentration data were analysed using a "one compartmental model with first-order elimination" to describe the pharmacokinetics of favipiravir using Microsoft Office Professional plus Excel 2013. As individual sampling time points may not necessarily occur at the true maximums, T_{max}, C_{max} and AUC values are reported based on calculation. T_{max} and C_{max} values were calculated respectively by the following formulae: log $(K_a/K_e)/(K_a - K_e)$ and (F^*D/V_d) * $(e - K_e$ * $T_{max})$, where K_a = absorption rate constant; K_e = elimination rate constant; F^* = fraction of extravascular dose of drug absorbed; D = dose; V_d = volume of distribution; T_{max} = time to maximum concentration; and C_{max} = maximum concentration.

2.5 | Statistics

Data were presented as frequency, percentages and median with 25th–75th percentiles. Continuous variables for two independent groups were compared with the Mann–Whitney U-test since the data did not follow a normal distribution. A *P*-value of <.05 was set as the level of statistical significance.

2.6 | Nomenclature of targets and ligands

Drug/molecular target nomenclature in this article conforms to the IUPHAR/BPS Guide to PHARMACOLOGY and The Guide to Pharmacology coronavirus information page.[12,13] Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2020/21.[13]

3 | RESULTS

3.1 | Patients

Of the 23 patients who gave their written consent, two were admitted to the intensive care unit before blood sampling was completed and thus data of 21 patients were included in the study. Demographic characteristics and comorbidities are presented in Table 1.

Sixteen patients (76.2%) were discharged from the hospital within a median of 8 days (range: 5–28 days). Five patients (23.8%) died in the hospital. The median time from favipiravir initiation to death was 15 days (range: 10–26 days).

3.2 | Favipiravir concentration–time profiles and pharmacokinetics

Following the loading dose on Day 1, favipiravir's median trough concentration on Day 2 (Day-2-$C_{0\text{-trough}}$) was 21.26 μg/mL (25th–75th percentiles 8.37–30.78 μg/mL) and showed considerable variation (Figure 1). Day-2-AUC following favipiravir administration of 600 mg maintenance dose was 345.6 μg.h/mL (25th–75th percentiles 193.0–666.9 μg/mL).

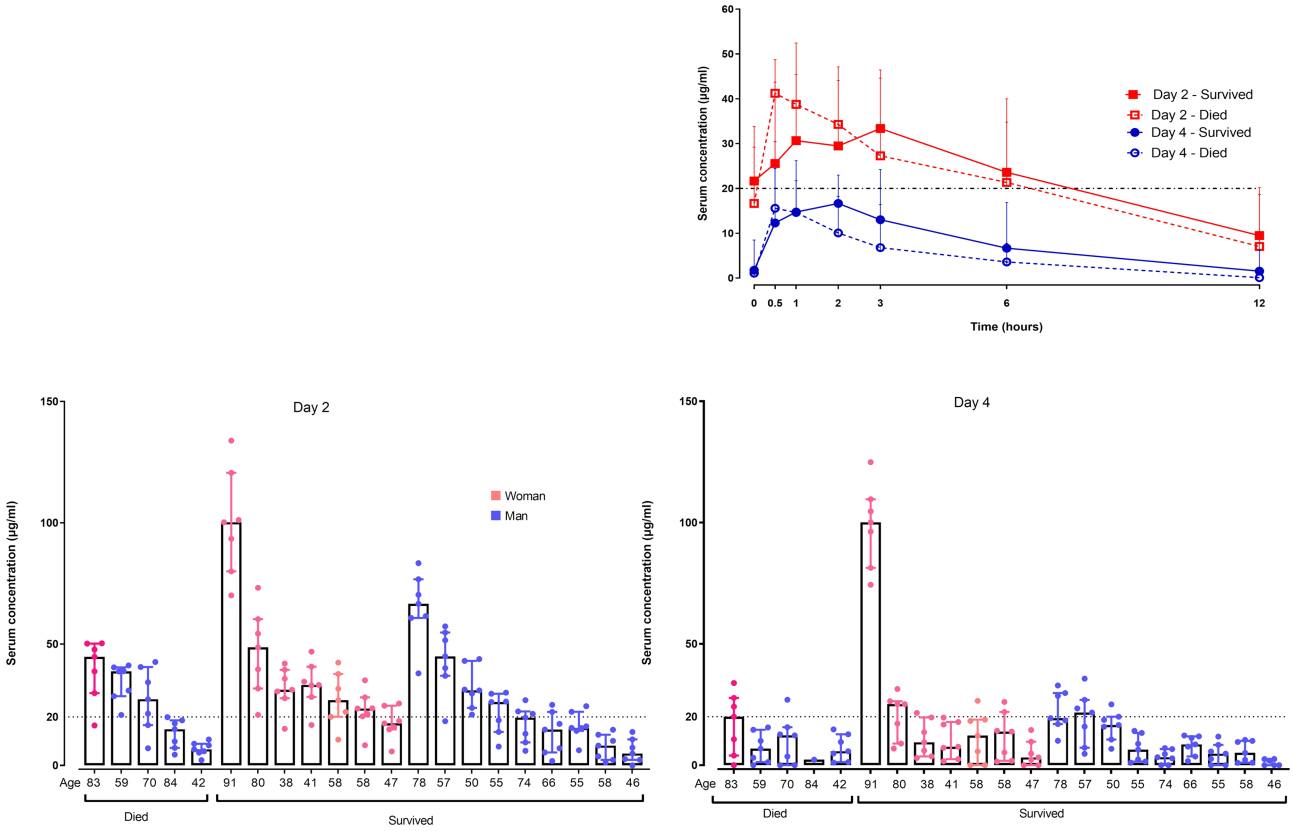

FIGURE 1 Favipiravir serum concentrations of each patient on Day 2 and Day 4. Serum concentration measurements at seven time points are represented by circles. Inset shows favipiravir serum concentration over time on Day 2 and Day 4. Data are presented as median with interquartile range

On Day 4 of treatment, a substantial decrease in favipiravir serum concentrations was observed. Day-4-$C_{0\text{-trough}}$ decreased by 89.0% to 1.61 µg/mL (0.0–6.4) and AUC decreased by 68.6% to 108.6 µg.h/mL (60.92–217.7) (Figure 1). C_{max}, T_{max}, $T_{½}$ and V_d decreased significantly and CL increased at Day 4 compared to Day 2 (Table 2). It is noteworthy that favipiravir Day-4-$C_{0\text{-trough}}$ concentrations were below the lower level of quantification (1 µg/mL) in six patients (28%) (Figure 1).

Women had significantly higher $C_{0\text{-trough}}$ levels than men on Day 2 ($P < .029$, Table 2). However, this difference was no longer significant ($P < .051$) when the concentrations were adjusted by the dose administered per unit weight. This difference was not present on the fourth day of treatment.

4 | DISCUSSION

In the present study we characterized the pharmacokinetics of favipiravir in 21 COVID-19 patients. We observed remarkable similarity between favipiravir trough concentration values on Day 2 as seen in patients treated for influenza.[3,14–17] Furthermore, in our study, mean favipiravir trough concentration values decreased by 89% between Day 2 (21.26 µg/mL) and Day 4 (1.6 µg/mL). However, several in vitro studies revealed favipiravir EC50 values > 9.4 µg/mL, and EC90 > 24.9 µg/mL to inhibit SARS-CoV-2.[18,19] Accordingly, the effective serum concentration of favipiravir for COVID-19 therapy is expected to be higher than these values, although there are no published favipiravir concentrations proven effective in the treatment of SARS-CoV-2 in humans. Pharmacokinetic data from previous studies revealed that favipiravir is 50% bound to plasma proteins.[3,4] Based on this assumption, total plasma concentration of the drug needs to be >20 µg/mL to achieve the EC50 value (9.4 µg/mL) for the free drug. Our results revealed that after 3 days, 52% of the patients had not received an adequate dose of medication to produce a serum concentration above 20 µg/mL at any time point. Given the massive impact of the global spread of COVID-19, our findings may provide valuable knowledge about therapies for this emerging disease, as well as aid in the preparation of new trials for dose modification that may be needed.[20,21]

The pharmacokinetics of favipiravir are sparsely reported and primarily entail healthy adult volunteers and some patients diagnosed with influenza.[4,8] The trough concentration of favipiravir in healthy subjects (Day 1: 1600 mg b.i.d., Days 2–5: 600 mg b.i.d.) ranged from 20 to 60 µg/mL. In contrast, the pharmacokinetics of favipiravir in hospitalized patients are somewhat different and the reasons for the difference are poorly understood.[9] In the data published by Irie et al.,[22] trough concentrations of favipiravir in patients administered the same drug regimen were mostly lower than the LOQ of 1 µg/mL.

TABLE 2 Favipiravir serum concentrations and pharmacokinetic parameters on Days 2 and 4 of treatment

		SURVIVED ($n = 16$)		DIED ($n = 5$)[a]			Male ($n = 13$)[a]		Female ($n = 8$)		
		Median	25th–75th percentile	Median	25th–75th percentile	*P*-value	Median	25th–75th percentiles	Median	25th–75th percentiles	*P*-value
Day 2	C_0	**21.66**	10.58–33.82	**16.64**	6.24–29.19	0.660	**13.8**	5.3–26.1	**28.8**	21.5–33.8	**0.029**
	C_{max}	**36.36**	25.68–44.23	**38.81**	16.29–47.53	0.735	**25.77**	18.07–43.38	**41.39**	36.36–52.52	0.115
	AUC	**374.80**	222.9–686.6	**305.10**	139.8–647.8	0.660	**231.5**	120.8–666.9	**550.4**	360.2–677.1	0.089
	CL	**8.59**	4.67–14.36	**10.49**	4.97–23.71	0.660	**13.82**	4.81–26.59	**5.83**	4.75–8.93	0.089
	$T_{1/2}$	**5.27**	4.41–6.78	**5.08**	4.15–8.47	0.999	**4.69**	3.53–7.45	**6.04**	4.72–6.62	0.301
	T_{max}	**1.92**	0.94–2.59	**1.49**	1.15–2.11	0.735	**1.42**	0.99–1.97	**2.08**	1.64–3.30	0.068
	V_d	**59.5**	48.81–105.3	**68.04**	59.61–128.3	0.398	**92.20**	59.61–129.3	**52.24**	44.14–60.08	**0.019**
Day 4	C_0	**1.77**	<1.00–8.49	**1.19**	<1.00–3.31	0.554	**1.19**	0–5.8	**3.1**	0.46–7.7	0.289
	C_{max}	**19.37**	12.68–28.98	**17.93**	12.32–25.76	0.736	**12.69**	12.01–27.22	**23.80**	18.44–30.19	0.091
	AUC	**111.80**	52.46–276.40	**77.94**	63.64–154.70	0.530	**71.8**	51.3–109.4	**153.6**	109.4–251.8	0.075
	CL	**10.73**	4.34–22.87	**15.49**	8.62–18.95	0.530	**16.71**	5.51–23.38	**7.90**	4.94–10.97	0.075
	$T_{1/2}$	**2.81**	2.16–4.65	**2.86**	2.13–3.44	0.665	**2.43**	2.08–4.26	**3.08**	2.39–4.35	0.717
	T_{max}	**1.21**	0.94–2.34	**1.05**	0.74–1.37	0.530	**1.02**	0.96–1.23	**1.57**	0.87–2.22	0.442
	V_d	**35.31**	32.18–79.46	**53.94**	35.67–78.42	0.597	**68.69**	33.90–82.83	**34.10**	30.23–38.36	**0.041**

[a]Day 4 concentration was missing in one participant.

In accordance with these findings, we observed favipiravir concentrations in hospitalized COVID-19 patients that were very low compared to previously published results in healthy subjects.[3,4] Additionally, mean favipiravir concentrations were significantly lower in male patients compared to those in female patients, but this difference was no longer significant when adjusted for dose per weight.

The concentration of favipiravir was very low, especially on the fourth day of therapy. Furthermore, median $C_{0\text{-trough}}$ values on Day 2 in the five patients who had died were lower than that of the 16 patients that survived (16.64 μg/mL *vs* 21.66 μg/mL). This difference was not statistically significant, possibly due to the low number of patients studied. However, this pattern leads us to believe that favipiravir concentration monitoring, and if possible, an increased dose on the fourth day, could be necessary, especially in COVID-19 patients showing no clinical improvement or with deterioration in the first 3 days of treatment. Since the effectiveness of antiviral agents is maximum when they are given in the first days of infection to intervene with the peak of viral replication, higher drug dosages could be considered to "hit early and hit hard".[23,24]

Although the primary target of our study was to describe the serum concentration–time profile and pharmacokinetic features of favipiravir, follow-up of the laboratory parameters of the COVID-19 patients indicated a significant increase in ferritin levels in the deceased patients, whereas there was a significant decrease in D-dimer and C-reactive protein levels in the surviving patients at Day 0 compared to Day 5. In previous studies, COVID-19 patients with elevated inflammatory markers have been reported to have worse prognosis of disease and our results are compatible with such findings in the literature.[10,18,23,25,26] A recent observation indicated a hyperinflammatory state in COVID-19, which is related to hyperdynamic state with high cardiac output and increased renal perfusion due to vasodilatation, which results in augmented renal clearance and speeds the elimination of renally cleared drugs.[19,27] Therefore, monitoring drug concentration of renally eliminated drugs can be advised in critically ill COVID-19 patients.[19]

Our data should be interpreted with caution since the sample size was small, which might have led to type 2 error. Also, due to the small sample size, we were not able to conduct multivariable analysis and adjust for confounders. The favipiravir dosage used, however, was clearly inadequate to achieve reasonable blood concentration.

Another point is that favipiravir is a pro-drug that is metabolized intracellularly to its active form F-RTP. In vitro and in vivo animal studies showed that there is a linear relationship between extracellular favipiravir concentration and intracellular levels of F-RTP.[19,27] Thus, in retrospect, it would have been valuable for us to have measured the active metabolite; however, we did not have enough serum.

In the light of these findings, trials involving a greater number of patients and additional favipiravir doses, particularly in patients who have not improved clinically after the third day, may be useful for determining the optimal dosage.[20] Given the massive effect of the global spread of COVID-19, our findings may provide valuable knowledge about therapies for this emerging disease, as well as aid in the preparation of new trials for dose modification that may be needed.

In conclusion, our results suggest that favipiravir pharmacokinetics exhibited marked variability among patients treated for COVID-19. Monitoring of serum favipiravir concentrations could be a reasonable consideration in guiding dosage regimens in individual patients as occurs with many drugs that are associated with marked pharmacokinetic variability.

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COMPETING INTERESTS

None of the authors declared any conflicts of interest.

CONTRIBUTORS

R.G., E.E., M.G.İ., P.A. and F.O. proposed the concept and were involved in the design of the study, analysis and interpretation of data, and preparation of the manuscript. A.K. and H.R.Y. participated in the design of the study. N.R. and M.G.İ. contributed to the pharmacokinetic analysis. P.A., Y.Ç. and R.G. performed statistical analysis. P.P. contributed to interpretation of the data, and preparation of the manuscript. Y.Ç. and A.T. contributed to the design of the study and acquisition of the data. D.K., Ş.O.Y., M.B.B., U.S., E.T., B.E.Ş., S.K. and V.K. participated in clinical evaluation and supervision of the patients. A.E., C.B., A.E.G. and M.H. developed the LC–MS/MS method for measurement of favipiravir concentrations. All authors reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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