BRIEF REPORT

Pharmacokinetics of Favipiravir in Critically Ill Patients With COVID-19

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Since December 2019, a novel coronavirus (severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)) infection has been rapidly spreading worldwide and causing the respiratory illness, coronavirus disease 2019 (COVID-19). The antiretroviral drug favipiravir (FPV) has been experimentally used for COVID-19 treatment since March 2020 in Japan. However, the pharmacokinetics of FPV in critically ill patients is unknown. We measured the serum concentration of FPV using high-performance liquid chromatography in patients with severe COVID-19 who were admitted to the intensive care unit and placed on mechanical ventilation. The patients were administered 1,600 mg of FPV twice daily on day 1, followed by 600 mg twice daily from day 2 to day 5 (or more if needed). Suspensions of FPV tablets were administered through a nasogastric tube. Seven patients were enrolled in this study. Forty-nine blood samples were obtained from the eligible patients to evaluate FPV concentration. The FPV trough (after 8–12 hours) concentrations of most samples were lower than the lower limit of quantification (1 µg/mL) and half-maximal effective concentration (9.7 µg/mL) against SARS-CoV-2 previously tested in vitro. FPV trough concentration in critically ill patients was much lower than that of healthy subjects in a previous clinical trial, which is a cause for great concern. Further study is required to determine the optimal strategy for treatment of patients with severe COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense single-stranded RNA virus that is closely related to bat-derived severe acute respiratory syndrome-like coronaviruses.1 Since its outbreak in Wuhan, China, in December 2019, the virus has rapidly spread worldwide and caused the respiratory illness, coronavirus disease 2019 (COVID-19).2 The symptoms of COVID-19 are generally mild; however, 6.1–14.2% of the patients, especially the elderly or those with complications, developed severe symptoms requiring admission to intensive care units (ICUs) and mechanical ventilation. Worsening of these symptoms resulted in death in 1.4–9.7% of patients with COVID-19.3,4 On April 28, 2020, ~211,000 people died of COVID-19 worldwide.5 In spite of ongoing clinical trials for combating COVID-19 with existing drugs (lopinavir/ritonavir, remdesivir, ciclesonide, chloroquine, and tocilizumab) and vaccines (mRNA-1237 and INO-4800), no specific treatment exists at this point.

In Japan, favipiravir (FPV) has been experimentally used for treating COVID-19 since March 2020. FPV is an RNA-dependent RNA polymerase inhibitor acting on a broad spectrum of various viral RNA polymerases.6,7 The drug was originally developed for resistant influenza virus infections. The use of FPV is restricted and it cannot be used without state permission in Japan.8,9 Not only is there no precedent for treatment of COVID-19 with FPV, but its clinical use has also been highly limited until now.

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A pharmacokinetic (PK) study of FPV in healthy subjects and few influenza patients was conducted during drug development.9 However, little is known about the PKs of FPV in critically ill patients admitted to ICUs and requiring invasive oxygenation. In ICU patients, PKs are dramatically changed owing to increased cardiac output, capillary leak, renal and hepatic clearance, and altered protein binding properties.10 The PK study of FPV in critically ill patients would support the efficacy and safety of the drug for treating COVID-19. Therefore, in this study, we evaluated the PK of FPV in patients with COVID-19 who were admitted to the ICU and placed on mechanical ventilation.

METHODS

Patients
Critically ill patients with COVID-19 who were admitted to the ICU on mechanical ventilation and administered FPV tablets (AVIGAN tablet 200 mg; Toyama Chemical, Tokyo, Japan) between March 19, 2020, and April 16, 2020, in Kobe City Medical Center General Hospital were eligible for this observational study. FPV was not approved for treatment of COVID-19 in Japan, and the efficacy and dosage were not established. Therefore, FPV was administered on a compassionate-use basis to the patients included in this study. Demographic and clinical characteristics, including age, sex, body mass index, aspartate aminotransferase, alanine aminotransferase, serum creatinine, comorbidities, other drugs for COVID-19, comedications, possible adverse drug reactions of FPV, and clinical status after starting FPV treatment were investigated. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Kobe City Medical Center General Hospital (Approval number: Zn200418, Approval date: March 31, 2020). All study participants or their families provided informed consent.

FPV administration
According to the dosage indicated for influenza, patients were administered 16.00 mg of FPV twice on day 1, followed by 600 mg twice daily from day 2 to day 5 (or more if needed). Patients on mechanical ventilation while in the ICU were administered suspensions of FPV tablets through nasogastric tubes. The suspensions were prepared by dissolving FPV tablets in water at 55°C. The administration procedure was followed as instructed by the manufacturer and stability was confirmed.

| Patient 1 78 Female 25.1 7/7/6 Chronic subdural hematoma, uterine fibroid Ciclesonide inhaler 34 30 0.48 |
|-----------------|------------------|-----------|---------------------|---------------------|
| Patient 2 75 Male NE 7/8/8 Hypertension, hyperlipidemia, benign prostatic hyperplasia, gout Ciclesonide inhaler 41 37 0.92 |
| Patient 3 75 Female NE 10/9/9 Parkinson’s disease, hypertension Ciclesonide inhaler 58 51 1.26 |
| Patient 4 76 Male 19.0 6/2/−1 Hypertension, prostate cancer, primary biliary cholangitis – 65 30 0.52 |
| Patient 5 66 Male 27.6 1/0/−1 Type 2 diabetes mellitus – 91 53 1.22 |
| Patient 6 41 Male 29.9 0/1/1 – – 85 69 1.01 |
| Patient 7 66 Male NE 0/0/0 Type 2 diabetes mellitus, hyperuricemia – 64 19 1.47 |

Clinical status after starting FPV with body temperature and PaO2/FiO2

| Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 7 | Day 14 |
|-------|-------|-------|-------|-------|-------|-------|
| 6 (37.4°C, 150)5 | 6 (37.7°C, 169) | 6 (37.1°C, 193) | 6 (37.4°C, 231) | 4 (37.7°C, 299) | 4 (36.9°C, 254) | 3 (36.7°C, NE) |
| 6 (38.0°C, 171) | 6 (37.9°C, 166) | 6 (37.0°C, 164) | 6 (37.4°C, 175) | 6 (38.4°C, 210) | 6 (38.5°C, 201) | 6 (37.6°C, 277) |
| 6 (39.0°C, 134) | 6 (38.7°C, 156) | 6 (39.2°C, 178) | 6 (38.9°C, 169) | 6 (38.1°C, 154) | 6 (37.7°C, 150) | 6 (38.6°C, 150) |
| 4 (39.5°C, 143) | 6 (38.9°C, 190) | 6 (38.5°C, 227) | 6 (38.6°C, 214) | 6 (39.2°C, 196) | 6 (38.5°C, 264) | 3 (36.6°C, NE) |
| 4 (39.2°C, 115) | 6 (39.3°C, 152) | 6 (39.7°C, 140) | 6 (38.7°C, 178) | 6 (39.0°C, 235) | 6 (39.7°C, 113) | 6 (38.4°C, 198) |
| 6 (38.8°C, 89) | 6 (38.2°C, 210) | 6 (38.9°C, 134) | 6 (39.5°C, 74) | 6 (39.8°C, 77) | 6 (38.6°C, 124) | 4 (37.4°C, 214) |
| 6 (38.8°C, 113) | 6 (39.8°C, 130) | 6 (39.2°C, 99) | 6 (38.2°C, 124) | 6 (38.3°C, 109) | 6 (38.0°C, 106) | 6 (40.0°C, 232) |

Clinical status (seven-category ordinal scale); (1) non-hospitalization, no limitation of activities; (2) non-hospitalization, limitation of activities; (3) hospitalization, not-required oxygen; (4) hospitalization, required oxygen by mask or nasal prongs; (5) hospitalization, required noninvasive ventilation and/or high-flow oxygen; (6) hospitalization, required oxygen (invasive) and/or extracorporeal membrane oxygenation; and (7) death.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COVID-19, coronavirus disease 2019; FPV, favipiravir; NE, not evaluated; SCr, serum creatinine.
5Days from COVID-19 diagnosis, Hospitalization, or admission to intensive care unit up to FPV initiation.
6Best score of clinical status (highest body temperature, lowest PaO2/FiO2) at each day.
Patients were administered many drugs, including antibiotics, opioids, analgesics, sedatives, and pressors during FPV treatment, but medications known to interact with FPV were avoided.

**FPV concentration**

Forty-nine samples were obtained from eligible patients to evaluate FPV concentrations. All FPV concentrations and the corresponding blood sampling time after FPV administration are summarized in Table 2. For example, the concentration after 8 hours from the first 1,600 mg dosing was "< 1.0" in patient 1. Most sample concentrations were lower than the LLOQ (1 µg/mL) and half-maximal effective concentration (9.7 µg/mL) against SARS-CoV-2 tested in vitro.11 Patients 4 and 5 presented remarkably high FPV concentrations before intubation on the first day, which then declined after intubation. Patient 1 was weaned from mechanical ventilation from day 5 onward, and the FPV concentration slightly increased on day 7 (2.7 µg/mL).

**Treatment outcome**

The best score of clinical status, highest body temperature, and lowest PaO2/FiO2 on each day after FPV administration are shown in Table 2. One of seven patients (14.3%) showed improvement and was weaned from mechanical ventilation 7 days after starting FPV. In addition, 3 of 7 patients (42.9%) improved and were weaned from mechanical ventilation after 14 days and 2 patients (28.6%) did not require oxygenation after 14 days. Mild aspartate aminotransferase increase was observed in patient 5 as an adverse event related to FPV, but multiple other drugs were suspected to cause this event.

**DISCUSSION**

In the present study, we evaluated FPV serum concentrations in critically ill patients with COVID-19 who were admitted to the ICU and required mechanical ventilation. The concentration was much lower than that previously reported in healthy subjects. According to the PK study (day 1: 1,600 mg b.i.d., day 2–5: 600 mg b.i.d.) in the AVIGAN package insert, FPV trough (after 12 hours) concentration in healthy subjects was 20–60 µg/mL.8,9 However, the trough concentrations (within 8–12 hours) in patients receiving the same regimen in this study were mostly lower than the LLOQ. This underexposure to FPV in severely ill patients with COVID-19 is of great concern as the half-maximal effective concentration (9.7 µg/mL) against SARS-CoV-2 tested in vitro11 is reportedly much higher than that against influenza virus.8 Two patients who were intubated after taking FPV orally had higher FPV concentrations than the other patients who were intubated with FPV. These observations suggest that exposure to FPV is different depending on the severity of illness, which is usually high in ICU-requiring patients.

A PK case study of FPV in patients with severe influenza needing continuous venovenous hemofiltration was reported. In the study, FPV was administered at 400 mg b.i.d. and the peak plasma concentration (Cmax) was only 4.43 µg/mL indicating increased distribution volume and clearance.12 PK of FPV was also studied in Ebola virus disease.
### Table 2  Favipiravir serum concentration in severely ill patients with COVID-19

| Patient 4 | 1,600 mg | 1,600 mg | 600 mg | 600 mg | 600 mg | 600 mg | 600 mg | 600 mg | 600 mg | 600 mg |
|-----------|----------|----------|--------|--------|--------|--------|--------|--------|--------|--------|
|           | Day 1    | Day 2    | Day 3  | Day 4  | Day 5  | Day 6  | Day 7  | Day 8  | Day 9  | Day 10  |
|           | 45.6, 38.8, 34.0 | 17.4, 16.8 | 8.8 | 5.3 | 2.4 | NA | NA | NA | NA | NA |
|           | (8, 9, 10 hours) | (10, 10.3 hours) | (13 hours) | (9 hours) | (11 hours) |
| Patient 6 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 |
|           | (12 hours) | (11 hours) | (11 hours) | (11 hours) | (11 hours) | (12 hours) | (12 hours) | (12 hours) | (12 hours) |
| Patient 7 | < 1.0 | 23 | 3 | < 1.0 | < 1.0, < 1.0 | < 1.0 | NA | NA | NA | NA |
|           | (1 hours) | (9 hours) | (12 hours) | (10 hours) | (10, 12 hours) | (11 hours) |

(i) indicates blood sampling time after administration.
COVID-19, coronavirus disease 2019; FPV, favipiravir; NA, not applicable.

FPV (1,600 mg) was taken twice orally on day 1.

| FPV concentration, µg/mL |
|--------------------------|
| Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 |
| 1,600 mg | 1,600 mg | 600 mg | 600 mg | 600 mg | 600 mg | 600 mg | 600 mg | 600 mg | 600 mg |
| < 1.0 | < 1.0 | < 1.0 | 2.7 | NA | NA | NA | NA |
| (8 hours) | (11 hours) | (11 hours) | (10 hours) | (11 hours) | (10 hours) |
| 2.5 | 1.2 | < 1.0 | < 1.0 | < 1.0 | NA | NA | NA | NA |
| (8 hours) | (12 hours) | (11 hours) | (11 hours) | (9 hours) |
| 3.9 | 5.5 | 1.7 | 2.4 | 3 | NA | NA | NA | NA |
| (10 hours) | (12 hours) | (11 hours) | (10 hours) | (9 hours) |
| Patient 6 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 | < 1.0 |
|           | (12 hours) | (11 hours) | (11 hours) | (11 hours) | (11 hours) | (12 hours) | (12 hours) | (12 hours) | (12 hours) |
| Patient 7 | < 1.0 | 23 | 3 | < 1.0 | < 1.0, < 1.0 | < 1.0 | NA | NA | NA |
|           | (1 hours) | (9 hours) | (12 hours) | (10 hours) | (10, 12 hours) | (11 hours) |
(JIKI study). In the JIKI study, FPV was used at doublet dos-
age (day 0: 6,000 mg, 2,400 mg, 2,400 mg, 1,200 mg q8h),
day 1–9: 1,200 mg b.i.d.) in adults. The median (min-max)
trough concentration was 46.1 µg/mL (2.3–106.9) on day 2
and 25.9 µg/mL (0–173.2) on day 4. The authors mentioned
that the unexpected drop between day 2 and day 4 could
be due to severe sepsis and/or the intrinsic properties of
FPV metabolism. The targeted FPV concentration was not
reached in the JIKI study.\textsuperscript{15} These results are consistent
with our findings in this study.

Many studies report increased drug distribution volume\textsuperscript{14,16} and increased clearance\textsuperscript{16,17} in ICU patients. In
addition, gastrointestinal absorption might be decreased
by the use of drugs, such as sedatives and opioids, which
reduce gastrointestinal motility. Previous studies on oral
drug formulations report decreased concentration when
administered through a nasogastric tube in critically ill pa-
tients.\textsuperscript{18,19} Therefore, FPV PK in ICU patients can be quite
different from that in healthy volunteers. Unlike general
septic shock, patients with severe COVID-19 present acute
respiratory distress syndrome pathology and need deep se-
dation and conservative fluid management to prevent lung
injury.\textsuperscript{20,21} Although the reason could not be confirmed be-
cause peak time-point concentrations were not obtained,
decreased drug absorption might be of greater concern
here. In addition, the suspension of FPV tablets showed
stability, but the bioavailability has not been confirmed. The
administration procedure of FPV tablet’s slurry requires fur-
ther examination. Furthermore, FPV is mainly metabolized
by aldehyde oxidase (AO) and exhibits nonlinear PK. The
trough concentration of FPV seems to increase with dose
and time-dependent “auto-inhibition of AO.”\textsuperscript{9,22} Many AO
substrates report poor PKs with rapid metabolism and failed
drug development.\textsuperscript{23–25} Therefore, the auto-inhibition of AO
is speculated to be necessary to maintain significant FPV
concentration.

Although some improvement was observed in 3 pa-
tients with COVID-19 by day 14, it is unclear how FPV
influenced this improvement. FPV is a prodrug that
undergoes metabolic activation through ribosylation
and phosphorylation to form the activated metabolite
T-705RTP in the tissues.\textsuperscript{22} Therefore, the tissue distribu-
tion or activated metabolite concentration in cells might
be different from the FPV trough concentrations observed.
The efficacy of FPV against COVID-19 should be deter-
ned in ongoing clinical trials. Treatment for patients with
severe COVID-19 is extremely limited now and of utmost
importance for reducing mortality. The FPV clinical trial
for critically ill patients with COVID-19 should be planned
with regard to dosage (to obtain auto-inhibition of AO and
sufficient FPV concentration) and formulation (i.e., if pos-
possible). Otherwise, we might underestimate the efficacy
of the limited drugs that show promise as a treatment for
COVID-19. This problem should be revived in the influenza
pandemics again.

In conclusion, FPV concentrations in critically ill patients
were much lower than that in healthy volunteers, which is
of great concern during treatment. Further study is required
to determine the optimal strategy for treatment of patients with
severe COVID-19.

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performed the research. K.I. analyzed the data.

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