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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.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Little is known about the pharmacokinetics (PKs) of favipiravir (FPV) in critically ill patients with coronavirus disease 2019 (COVID-19) admitted to intensive care units and requiring invasive oxygenation as the clinical use of FPV has been limited and has no precedent in treating COVID-19.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The PKs of FPV was evaluated in patients with severe COVID-19 to reveal the clinical outcomes.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ FPV trough concentration in critically ill patients was much lower than that of healthy subjects in a previous clinical trial.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ It may help with planning the FPV clinical trial for critically ill patients with COVID-19 with regard to the optimal dosage and formulation.

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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Table 1 Patients' baseline characteristics before initiation of FPV and treatment outcome

	Age	Sex	BMI	Time after COVID-19 diagnosis/ Hospitalization/ICU admission (days)[a]	Comorbidities	Other drugs for COVID-19	AST (IU)	ALT (IU)	SCr (mg/dL)
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 PaO_2/FiO_2						
Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 7**	**Day 14**
6 (37.4°C, 150)[b]	6 (37.7°C, 169)	6 (37.1°C, 193)	6 (37.7°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 (36.8°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 (38.6°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.
[a]Days from COVID-19 diagnosis, Hospitalization, or admission to intensive care unit up to FPV initiation.
[b]Best score of clinical status (highest body temperature, lowest PaO_2/FiO_2) at each day.

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.

Pharmacokinetic sampling

Blood samples (serum) were obtained daily from the patients. The times when FPV was administered and blood samples were obtained were recorded. The serum samples were stored at –20°C until measurement and handled only when wearing personal protective equipment.

Pharmacokinetic measurement

Bulk powder of FPV were purchased from Selleck Chemicals (Houston, TX). Serum concentrations of FPV were measured by Agilent 1200 high-performance liquid chromatography system (Agilent, Waldbronn, Germany). The linear calibration range of FPV was 1–100 μg/mL (R^2 > 0.999), and the lower limit of quantification (LLOQ) was 1 μg/mL. The intra-assay accuracy (relative error %, n = 5) and precision (relative SD %, n = 5) were 1.9–4.9% and 90.1–96.4%, respectively. The inter-assay accuracy and precision (n = 3) were 0.3–1.4% and 95.1–100.5%, respectively. FPV was stable in serum at 25°C for 48 hours and at –20°C for 7 days.

Clinical status after starting FPV

The clinical status after starting FPV was evaluated on days 1–5, day 7, and day 14 by a 7-category ordinal scale as follows:

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.
7. Death.

Body temperature and PaO_2/FiO_2 were also studied each day. PaO_2/FiO_2 was defined as the ratio of the partial pressure of arterial oxygen to the percentage of inspired oxygen.

RESULTS

Patients' baseline characteristics

Seven patients were included in this observational study. Their baseline characteristics before FPV initiation are summarized in **Table 1**. All the patients were diagnosed with COVID-19 using real-time polymerase chain reaction-tested nasopharyngeal swabs and radiography imaging. Median (range) days from COVID-19 diagnosis, hospitalization, and admission to ICU up to FPV initiation were 6 days (0–10), 2 days (0–9), and 1 day (–1 to 9), respectively. Five patients were admitted to the ICU and placed on mechanical ventilation before treatment with FPV. Two patients (4 and 5) were orally administered FPV (1,600 mg) twice and then admitted to the ICU for intubation. Patients placed on mechanical ventilation were administered FPV through nasogastric tubes and patient 1 continued to receive FPV through a nasogastric tube even after extubation. Patients 1 and 6 were administered FPV for 7 and 10 days, respectively, whereas the other patients were administered FPV for 5 days. The 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 PaO_2/FiO_2 on each day after FPV administration are shown in **Table 1**. 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 vitro*[11] is reportedly much higher than that against influenza virus.[9] 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 (C_{max}) 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

	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	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg
Patient 1	< 1.0 (8 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (12 hours)		< 1.0 (10 hours)		< 1.0 (11 hours)		2.7 (10 hours)		NA		NA		NA	
Patient 2	2.5 (8 hours)		1.2 (12 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (9 hours)		NA		NA		NA		NA		NA	
Patient 3	3.9 (10 hours)		5.5 (12 hours)		1.7 (11 hours)		2.4 (10 hours)		3 (9 hours)		NA		NA		NA		NA		NA	
Patient 4[a]		45.6, 38.8, 34.0 (8, 9, 10 hours)		17.4, 16.8 (10, 10.3 hours)		8.8 (13 hours)		5.3 (9 hours)		2.4 (11 hours)	NA		NA		NA		NA		NA	
Patient 5[a]		41.6 (6 hours)	25.8 (6 hours)	5.6 (11 hours)		< 1.0 (11 hours)		2.8, < 1.0 (5, 11 hours)		< 1.0 (10 hours)	NA		NA		NA		NA		NA	
Patient 6	< 1.0 (12 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (12 hours)		< 1.0 (10 hours)		< 1.0 (12 hours)		< 1.0 (12 hours)	
Patient 7	< 1.0 (1 hours)	23 (9 hours)		3 (12 hours)		< 1.0 (10 hours)		< 1.0, < 1.0 (10, 12 hours)		< 1.0 (11 hours)	NA		NA		NA		NA		NA	

() indicates blood sampling time after administration.
COVID-19, coronavirus disease 2019; FPV, favipiravir; NA, not applicable.
[a]FPV (1,600 mg) was taken twice orally on day 1.

(JIKI study). In the JIKI study, FPV was used at doublet dosage (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.[13] These results are consistent with our findings in this study.

Many studies report increased drug distribution volume[14,15] and increased clearance[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 patients.[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 sedation and conservative fluid management to prevent lung injury.[20,21] Although the reason could not be confirmed because 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 further 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."[9,22] Many AO substrates report poor PKs with rapid metabolism and failed drug development.[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 patients 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.[22] Therefore, the tissue distribution or activated metabolite concentration in cells might be different from the FPV trough concentrations observed. The efficacy of FPV against COVID-19 should be determined 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.v., if 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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1. Lu, R. *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* **395**, 565–574 (2020).
2. Spinelli, A. & Pellino, G. COVID-19 pandemic: perspectives on an unfolding crisis. *Br. J. Surg.* **107**, 785–787 (2020).
3. Zhou, F. *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* **395**, 1054–1062 (2020).
4. Richardson, S. *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* **323**, 2052–2059 (2020).
5. Coronavirus COVID-19 Global Cases by Johns Hopkins The Center for Systems Science and Engineering (CSSE). <https://coronavirus.jhu.edu/map.html>. Accessed April 28, 2020.
6. Delang, L., Abdelnabi, R. & Neyts, J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. *Antiviral Res.* **153**, 85–94 (2018).
7. 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.* **93**, 449–463 (2017).
8. Package insert Avigan Tablet 200 mg (English translation) by Toyama Chemical Co., Ltd., November 2017. <https://www.cdc.gov.tw/File/Get/ht8jUiB_MI-aKnlwstwzvw>. Accessed April 25, 2020.
9. Report on the Deliberation Results Avigan Tablet 200 mg by Pharmaceuticals and Medical Devices Agency (PMDA), March 4, 2014. <https://www.pmda.go.jp/files/000210319.pdf>. Accessed April 25, 2020.
10. Roberts, J.A. & Lipman, J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. *Clin. Pharmacokinet.* **45**, 755–773 (2006).
11. Wang, M. *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* **30**, 269–271 (2020).
12. Favie, L.M., Murk, J.L., Meijer, A., Nijstad, A.L., van Maarseveen, E.M. & Sikma, M.A. Pharmacokinetics of favipiravir during continuous venovenous haemofiltration in a critically ill patient with influenza. *Antivir. Ther.* **23**, 457–461 (2018).
13. Nguyen, T.H. *et al.* Favipiravir pharmacokinetics in Ebola-infected patients of the JIKI trial reveals concentrations lower than targeted. *PLoS Negl. Trop. Dis.* **11**, e0005389 (2017).
14. Couffignal, C. *et al.* Population pharmacokinetics of imipenem in critically ill patients with suspected ventilator-associated pneumonia and evaluation of dosage regimens. *Br. J. Clin. Pharmacol.* **78**, 1022–1034 (2014).
15. Fernandez de Gatta, M.M., Mendez, M.E., Romano, S., Calvo, M.V., Dominguez-Gil, A. & Lanao, J.M. Pharmacokinetics of amikacin in intensive care unit patients. *J. Clin. Pharm. Ther.* **21**, 417–421 (1996).
16. Pujal, M., Soy, D., Codina, C. & Ribas, J. Are higher vancomycin doses needed in ventricle-external shunted patients? *Pharm. World Sci.* **28**, 215–221 (2006).
17. Pea, F., Di Qual, E., Cusenza, A., Brollo, L., Baldassarre, M. & Furlanut, M. Pharmacokinetics and pharmacodynamics of intravenous levofloxacin in patients with early-onset ventilator-associated pneumonia. *Clin. Pharmacokinet.* **42**, 589–598 (2003).
18. Tang Girdwood, S.C. *et al.* Route of oseltamivir administration affects metabolite concentrations in critically ill children. *Pediatr. Infect. Dis. J.* **38**, 1224–1227 (2019).
19. Ray, J., Campbell, L., Rudham, S., Nguyen, Q. & Marriott, D. Posaconazole plasma concentrations in critically ill patients. *Ther. Drug Monit.* **33**, 387–392 (2011).
20. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance 2020. <https://www.who.int/publications-detail/clinical-management-of-severe-acute respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected>. Accessed April 25, 2020.
21. National Heart, L. *et al.* Comparison of two fluid-management strategies in acute lung injury. *N. Engl. J. Med.* **354**, 2564–2575 (2006).

22. Du, Y.X. & Chen, X.P. Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. *Clin. Pharmacol. Ther.* https://doi.org/10.1002/cpt.1844.
23. Manevski, N., King, L., Pitt, W.R., Lecomte, F. & Toselli, F. Metabolism by aldehyde oxidase: drug design and complementary approaches to challenges in drug discovery. *J. Med. Chem.* **62**, 10955–10994 (2019).
24. Jensen, K.G. *et al.* Lack of exposure in a first-in-man study due to aldehyde oxidase metabolism: investigated by use of 14C-microdose, humanized mice, monkey pharmacokinetics, and in vitro methods. *Drug Metab. Dispos.* **45**, 68–75 (2017).
25. Akabane, T., Tanaka, K., Irie, M., Terashita, S. & Teramura, T. Case report of extensive metabolism by aldehyde oxidase in humans: pharmacokinetics and metabolite profile of FK3453 in rats, dogs, and humans. *Xenobiotica* **41**, 372–384 (2011).

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