Favipiravir: Pharmacokinetics and Concerns About Clinical Trials for 2019-nCoV Infection

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An outbreak of 2019-nCoV infection has spread across the world. No specific antiviral drugs have been approved for the treatment of COVID-2019. In addition to the recommended antiviral drugs, such as interferon-α, lopinavir/ritonavir, ribavirin, and chloroquine phosphate, some clinical trials focusing on virus RNA-dependent RNA polymerase (RdRp) inhibitors have been registered and initiated. Favipiravir, a purine nucleic acid analog and potent RdRp inhibitor approved for use in influenza, is also considered in several clinical trials. Herein, we summarized the pharmacokinetic characteristics of favipiravir and possible drug–drug interactions from the view of drug metabolism. We hope this will be helpful for the design of clinical trials for favipiravir in COVID-2019, as data regarding *in vitro* virus inhibition and efficacy in preclinical animal studies are still not available.

An outbreak of 2019-novel coronavirus (nCoV) infection, a diseased called the new coronavirus pneumonia (NCP) by the Chinese government and later named as COVID-19 by the World Health Organization (WHO) on February 11, 2020, has spread across the world since the first case in December 2019 from Wuhan, China. As of April 1, 2020, 874,151 cases have been diagnosed worldwide, and 43,804 have died from the pandemic. However, no specific antiviral drugs have been approved for the treatment of COVID-19. Interferon-α, lopinavir/ritonavir, ribavirin, chloroquine phosphate, arbidol, and combinations of these drugs are recommended by the seventh update of the Chinese National Health Commission's Treatment Regimen. In the meantime, other possible urgent prevention and treatment options are discussed elsewhere.[1,2] Currently, there are > 100 clinical trials designed to test pre-existing US Food and Drug Administration (FDA) approved drugs and experimental antiviral agents, which have been proved to be safe and effective in other viral infections.

Additionally, traditional Chinese medicines have been registered at the time of the submission of this manuscript. Favipiravir is one of the antiviral candidates involved in the clinical trials.[3] To provide useful information for the dosing regimen and study design with favipiravir, a mini-review focused on the pharmacokinetic characteristics of favipiravir and the potential drug–drug interactions (DDIs) is presented here.

ANTIVIRAL TREATMENT FOR COVID-19 AND POTENTIAL USE OF FAVIPIRAVIR

Favipiravir (T705), a purine nucleic acid analog, is one of the antiviral candidates considered in several clinical trials (**Table 1**) to evaluate the safety and efficacy in patients with NCP. Emergency approval of favipiravir (formulation: tablet, 0.2 g) for a clinical trial in adult patients with NCP (2020L00005) was also announced by the National Medical Products Administration (NMDA) in China.

Favipiravir is a pyrazine carboxamide derivative (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) and a broad-spectrum antiviral drug approved in Japan for the treatment of influenza.[4] Favipiravir is a prodrug that is ribosylated and phosphorylated intracellularly to form the active metabolite favipiravir ibofuranosyl-5′-triphosphate (T-705-RTP).[4] T-705-RTP competes with purine nucleosides and interferes with viral replication by incorporation into the virus RNA and thus, potentially inhibiting the RNA dependent RNA polymerase (RdRp) of RNA viruses (**Figure 1**).[5] T-705-RTP inhibits RdRp of the influenza virus with an half-maximal inhibitory concentration (IC_{50}) of 0.022 μg/mL, but does not affect the human DNA polymerases α, β, and γ subunits at up to 100 μg/mL.[5] In addition to the inhibition of influenza virus, favipiravir shows inhibitory effects on a wide range of RNA viruses, such as arenavirus, bunyavirus, flavivirus, and filoviruses causing hemorrhagic fever.[4] During the 2014–2015 Ebola virus (EBOV) outbreak initiated in West Africa, a proof-of-concept trial with favipiravir was carried out in Guinea, and patients treated with favipiravir showed a trend toward improved survival.[6] In patients with an initial diagnosis of Ct ≥ 20 for the EBOV RNA, on-trial mortality was 20.0% (95% confidence interval 11.6–32.4), which was 33% lower than the target value (30%). A retrospective analysis of patients with Ebola virus disease (EVD) indicated that, in comparison with patients who received the WHO-recommended supportive therapy, those who accepted additional favipiravir treatment showed a higher overall survival rate and longer average survival time, and a higher percentage of patients with a > 100-fold viral load reduction.[7] Genome sequencing of the 2019-nCoV identified the virus as a single-stranded RNA beta-coronavirus with the *RdRp* gene

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[Correction added on 30 April 2020, after first online publication: The first sentence in Abstract has been changed to 'An outbreak of 2019-nCoV infection has spread across the world'].

Linked article: This article is linked to Letter to the Editor by Eloy, P. *et al., Clin. Pharmacol. Ther.* **108**, 188 (2020) https://doi.org/10.1002/cpt.1877 and Response Letter to Editor by Du, Y.-X. and Chen, X.-P. *Clin. Pharmacol. Ther.* **108**, 190 (2020) https://doi.org/10.1002/cpt.1878.

Received March 2, 2020; accepted April 2, 2020. doi:10.1002/cpt.1844

Table 1 Registered clinical trials with favipiravir for the treatment of COVID-19

Registration number	Design	Intervention	Outcomes
ChiCTR2000029544	Randomized controlled trial	Group A (*n* = 10): Current antiviral treatment plus BaloxavirMarboxil tablets. Group B (*n* = 10): Current antiviral treatment plus favipiravir tablets. Group C (*n* = 10): Current antiviral treatment.	1. Time to viral negativity by RT-PCR. 2. Time to clinical improvement.
ChiCTR2000029548	Randomized, open-label, controlled trial	Group A (*n* = 10): BaloxavirMarboxil: 80 mg on day 1, 80 mg on day 4; 80 mg on day 7 as necessary. No more than 3 times administration in total. Group B (*n* = 10): Favipiravir: 600 mg t.i.d. with 1,600 mg first loading dosage, no more than 14 days. Group C (*n* = 10): Lopinavir-Ritonavir: 200 mg/50 mg, twice daily, for 14 days.	1. Time to viral negativity by RT-PCR. 2. Time to clinical improvement: Time from start of study drug to hospital discharge or to NEWS < 2 for 24 hours.
ChiCTR2000029600	Nonrandomized controlled trial	Group A (*n* = 30): Alpha-interferon atomization. Group B (*n* = 30): Lopinavir and Ritonavir plus alpha-interferon atomization. Group C (*n* = 30): Favipiravir plus alpha-interferon atomization.	1. Declining speed of SARS-CoV-2 by PCR. 2. Negative time of SARS-CoV-2 by PCR. 3. Incidence rate of chest imaging. 4. Incidence rate of liver enzymes. 5. Incidence rate of kidney damage.
ChiCTR2000029996	Randomized controlled trial	Group A (*n* = 20): Favipiravir tablets; 200 mg; oral; twice a day. The adult dose is 1,600 mg per time on first day; the duration of treatment will be 10 days. Group B (*n* = 20): Favipiravir tablets; 200 mg; oral; twice a day. The adult dose is 1,800 mg per time on the first day; the duration of treatment will be 10 days. Group C (*n* = 20): Favipiravir tablets; 200 mg; oral; twice a day. The adult dose is 2,400 mg per time on first day; the duration of treatment will be 10 days.	1. Time to clinical recovery.
ChiCTR2000030113	Randomized controlled trial	Group A (*n* = 15): Keep ritonavir/ritonavir treatment. Group B (*n* = 15): Favipiravir.	1. Blood routine tests. 2. Liver function examination. 3. Renal function examination. 4. Blood gas analysis. 5. Chest CT examination.
ChiCTR2000030254	Randomized controlled trial	Group A (*n* = 120): Favipiravir tablets. Group B (*n* = 120): Arbidol tablets.	1. Clinical recovery rate of day 7.
ChiCTR2000030894	Randomized controlled trial	Group A (*n* = 90): Favipiravir combined with Tocilizumab. Group B (*n* = 30): Favipiravir. Group C (*n* = 30): Tocilizumab.	1. Clinical cure rate.
ChiCTR2000030987	Randomized controlled trial	Group A (*n* = 50): The oral trial drug favipiravir tablets plus chloroquine phosphate tablets. Group B (*n* = 50): Oral trial drug favipiravir tablets. Group C (*n* = 50): Oral placebo treatment.	1. Improvement or recovery of respiratory symptoms. 2. Viral nucleic acid shedding.

CT, computed tomography; NEWS, national early warning score; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

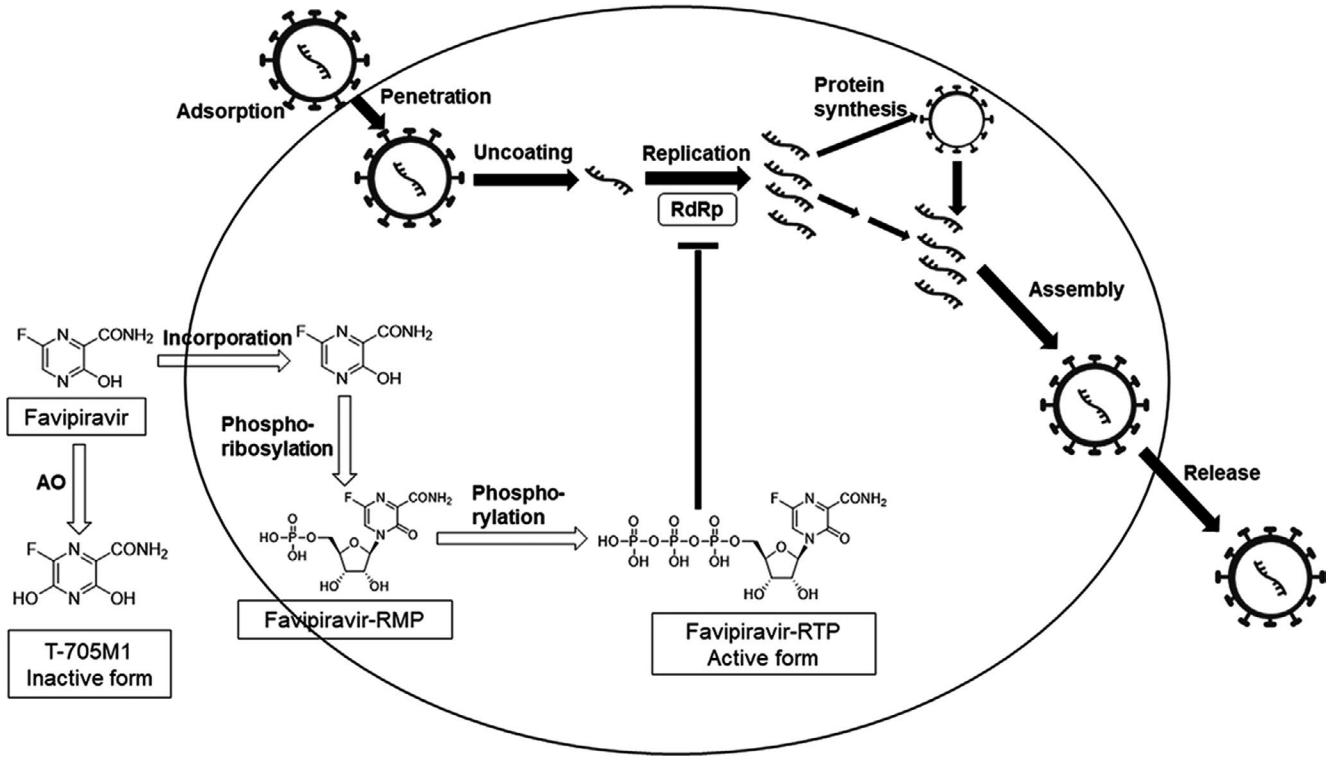

Figure 1 Mechanism of action of favipiravir (T-705) against the virus. Favipiravir is incorporated into cells and converted to favipiravir ibofuranosyl-5′-triphosphate (favipiravir-RTP) by host cells. The triphosphate form, favipiravir-RTP, inhibits the activity of RNA dependent RNA polymerase (RdRp) of RNA viruses. AO, aldehyde oxidase; RMP, ribosyl monophosphate.

similar to those of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) SARS-CoV-2 and Middle East respiratory syndrome coronavirus 2 (MERS-CoV-2).[8–10] Therefore, favipiravir is considered as one of the potential candidates for COVID-19,[2] although confirmed *in vitro* and preclinical animal studies are not available yet. A clinical trial to evaluate the safety and efficacy of favipiravir in the treatment of COVID-19 (ChiCTR2000029600) was conducted in Shenzhen, with 80 patients recruited.[11] The results showed that the 35 patients in the favipiravir arm demonstrated significantly shorter viral clearance time as compared with the 45 patients in the control arm (median 4 days vs. 11 days). X-ray examinations confirmed a higher rate of improvement in chest imaging in the favipiravir arm (91.43% vs. 62%).[11] A multicentered randomized clinical study (ChiCTR200030254) also suggested effective control of favipiravir on COVID-19.[12] For ordinary patients with COVID-19, 7 day's clinical recovery rate increased from 55.86% to 71.43% with favipiravir treatment. For ordinary patients with COVID-19 and patients with hypertension and/or diabetes, the time of fever reduction and cough relief in the favipiravir treatment group was also decreased significantly.[12]

PHARMACOKINETICS OF FAVIPIRAVIR

Studies from healthy Japanese volunteers showed that the maximum plasma concentration of favipiravir occurred at 2 hours after oral administration, and then decreased rapidly with a short half-life time of 2–5.5 hours.[13] The plasma protein binding of favipiravir was 54% in humans.[14] The bound percentages of favipiravir to human serum albumin and α1-acid glycoprotein were 65.0% and 6.5%, respectively.[15] The parent drug undergoes metabolism in the liver mainly by aldehyde oxidase (AO), and partially by xanthine oxidase, producing an inactive oxidative metabolite T-705M1 excreted by the kidneys.[13] The rapid appearance of favipiravir in the liver, followed by the gall bladder and segments of the intestinal tract after venous injection in mice, suggests rapid excretion of favipiravir by the liver in mice.[16] Pharmacokinetic analysis of intravenous favipiravir in cynomolgus macaques after repeated doses indicates obvious nonlinear pharmacokinetics over time and over a range of doses, and a continuous decline in plasma concentration after 7 days of continuous administration in the nonhuman primates is also observed.[17] Data obtained from 66 patients for experimental treatment with favipiravir for EVD (named as the JIKI trial) indicated that the steady-state trough concentration notably decreased on day 4 (25.9 μg/mL) as compared with day 2 (46.1 μg/mL), which supports a decrease in drug concentration after continuous use.[18]

To further understand the *in vivo* biodistribution and kinetics of uptake and clearance of favipiravir after a single and repeated administration, an ^{18}F radiolabeled favipiravir ([^{18}F]favipiravir) was developed.[16] Dynamic distribution of [^{18}F]favipiravir was assessed by positron emission tomography dynamic scans and gamma counting in naïve mice and favipiravir predosed mice (oral administration, loading dose: 250 mg/kg b.i.d., day 1; maintaining dose: 150 mg/kg, twice daily for 3 days) as well. In naïve mice, tail venous injection of [^{18}F]favipiravir resulted in rapid uptake and clearance through the liver, kidneys, and intestine. In contrast, in the predosed mice, the plasma concentration decreased by 25–50% and tissue distributions in the liver, stomach,

brain, and muscle tissue increased 2–5 times.[16] On the assumption that tissue retention of favipiravir is dependent on its ribosylated and phosphorylated form, the increased distribution by predosing or chronic use is supposed to promote cellular uptake and the antiviral efficacy of the drug. *In vitro* study indicates that favipiravir can inhibit AO activity in concentration-dependent and time-dependent manners, which explains self-inhibition of the inactivation metabolism of the parent drug and increased plasma parent/inactive metabolite ratio (T705/T705M1) after chronic dosing.[13] An increase in circulating T-705/T-705M1 ratio in mice is supposed to facilitate the cellular uptake and trapping of favipiravir in the tissue by increasing the extracellular to an intracellular concentration gradient.[16] This helps explain the accelerated circulating clearance of favipiravir after repeated administration. However, solid evidence from monitoring the tissue levels of T-705-RTP during continuous favipiravir use is warranted. T-705-RTP is also formed in human peripheral blood mononuclear cells (PBMCs),[13] and terminal half-life ($t_{1/2}$) of T-705-RTP was about 2 hours in PBMCs. Although $t_{1/2}$ of T-705-RTP in PBMCs was shorter than that in the lung ($t_{1/2}$ of about 4.2 hours),[15] we suggest that detection of T-705-RTP in PBMCs may serve as a surrogate considering the availability of peripheral blood.

THE DOSING REGIMEN OF FAVIPIRAVIR IN COVID-19

Dosing regimen is critical in clinical trials for antiviral purposes. The IC_{50} of favipiravir varies from nanomolar to micromolar concentrations depending on viral studies.[4] Therefore, dosage requirements and regimens may be different among treatments. The approved favipiravir regimen for influenza in Japan includes a 3,200 mg oral loading dose (1,600 mg every 12 hours) on day 1, followed by 600 mg twice daily on days 2–5.[19] Higher regimen (1,800 mg twice daily on day 1 followed by 800 mg twice daily thereafter) is also adopted in phase III.[19] Safety and efficacy of this regimen in influenza has been confirmed.[13] The main adverse reactions include mild to moderate diarrhea, an asymptomatic increase of blood uric acid and transaminases, and a decrease in the neutrophil counts.[13] Favipiravir dosage regimen for the treatment of EBOV infection in the JIKI trial and the targeted concentrations were estimated based on *in vitro* experiment (99% inhibitory concentration 29 μg/mL), preclinical data in the mouse model (150 mg/kg every 12 hours led to an average concentration of 59 μg/mL), 54% plasma protein binding in humans, and a pharmacokinetic model assessed with PK parameters estimated in healthy volunteers.[14] A 6,000 mg (2,400 mg, 2,400 mg, and 1,200 mg q8h) loading dose on day 1 followed by a 2,400 mg maintenance dose (1,200 mg q12h) on day 2 to day 9 was well tolerated.[18] The mean steady-state trough concentration was 46.1 μg/mL on day 2 (48 hours after the initial dose) and fell to 25.9 μg/mL on day 4 (96 hours after the initial dose).[18] Both of these concentrations were significantly lower than the predicted targeted concentrations of 54.3 and 64.4 μg/mL, respectively.[18] Regardless, the trial provided a reference to evaluate the efficacy of favipiravir in patients with COVID-19 in a circumstance without the preliminary *in vitro* and preclinical data. The up-to-date clinical study from China showed that the regiment of 3,200 mg (1,600 mg twice daily) loading dose on day 1 followed by 1,200 mg maintenance dose (600 mg twice daily) on day 2 to day 14 is effective.[11] Of note, previous clinical trials suggest that the plasma concentration of favipiravir in patients in the United States is 50% of that in Japanese patients,[13] suggesting a possible ethnic or regional difference in its pharmacokinetics, which should not be ignored. As data concerning the concentrations of the activated metabolite T-705RTP in the tissues and the inactivated metabolite T705M1 in plasma for these populations are not available, it is difficult to infer whether the difference in plasma concentration of favipiravir was resulted from differential tissue distribution or metabolic inactivation in the liver, or even differential absorption after oral administration.

REGARDING POTENTIAL DRUG–DRUG INTERACTION IN PHARMACOKINETICS

Multiple drug use is inevitable in the treatment of COVID-19, especially for patients with basic diseases (hypertension, diabetes, and cardiovascular diseases) and complications (such as acute respiratory distress syndrome, shock, arrhythmia, and acute kidney injury) commonly observed in the patients with COVID-19.[20,21] DDI is a topic that requires attention in clinical practice. Information about DDI caused by favipiravir is limited at present. Favipiravir is metabolized in the liver by AO in the cytosol, but not by enzymes in the microsomes. Published data are not available as to whether favipiravir and the active metabolite T-705-RTP affect activities of the hepatic drug-metabolizing enzymes. A previous study in healthy volunteers showed that concomitant administration of favipiravir increased the area under the curve (AUC) of acetaminophen and acetaminophen glucuronide by 20% and 23–34%, respectively, whereas the AUC of acetaminophen sulfate decreased by 29–35%, and the excretion of acetaminophen and the acetaminophen glucuronide increased in urine.[22] Co-incubation of favipiravir with human liver S9 inhibits acetaminophen sulfate formation with an IC_{50} value of 24 μg/mL, suggesting inhibition on the sulfate transferase.[22] When combined with favipiravir, the recommended maximum daily doses of acetaminophen are 3 g.

In vitro study demonstrates that selective estrogen receptor modulators (raloxifene, tamoxifen, and estradiol), the H2 receptor antagonist cimetidine, calcium channel blockers (felodipine, amlodipine, and verapamil), the anti-arrhythmic drug propafenone, and the tricyclic antidepressant amitriptyline are potent AO inhibitors (**Table 2**).[23] Although the clinically relevant DDI based on AO inhibition has yet to be established, an obvious DDI between cimetidine and zaleplon is reported.[24] Cimetidine coadministration results in a marked inhibition on AO catalyzed oxozaleplon formation and a warning is included in the zaleplon label.[25] Potential DDIs between these drugs and favipiravir should be carefully monitored. Several drugs, such as citalopram,[26] zaleplon,[27] famciclovir,[28] and sulindac,[29] are also metabolized by AO. *In vitro* study shows that favipiravir is a mechanism based inhibitor of AO in a concentration-dependent manner between 3.14 and 942 μg/mL[15] and the previous clinical study showed a mean steady-state trough concentration of 46.1 μg/mL in the treatment of EVD.[18] Therefore, potential DDIs between favipiravir and these latter drugs should also be monitored with caution.

Table 2 Inhibition of drugs and xenobiotics on human AO at 50 μM and the IC_{50} values

Drug	Indication or use	Percentage of control activity (mean ± SD)	IC_{50} (μM) (mean ± SE)
Raloxifene	Antiosteoporotic	<1.0	0.0029 ± 0.0003
Perphenazine	Antipsychotic	1.2 ± 0.2	0.033 ± 0.011
Thioridazine	Antipsychotic	7.1 ± 3.9	0.16 ± 0.07
Menadione	Prothrombogenic	4.1 ± 0.5	0.20 ± 0.04
Trifluoperazine	Antipsychotic	8.0 ± 1.9	0.24 ± 0.08
Amitriptyline	Antidepressant	9.4 ± 4.7	0.26 ± 0.07
Estradiol	Estrogen	7.4 ± 3.3	0.29 ± 0.07
Felodipine	Antihypertensive/anti-anginal	7.0 ± 5.4	0.30 ± 0.08
Clomipramine	Antidepressant	18 ± 6	0.48 ± 0.17
Loratadine	Antihistaminic	7.3 ± 1.4	0.49 ± 0.13
Promethazine	Antipsychotic	10 ± 3	0.51 ± 0.26
Chlorpromazine	Antipsychotic	3.1 ± 2.5	0.57 ± 0.15
Ethinyl estradiol	Oral contraceptive	6.2 ± 8.1	0.57 ± 0.15
Norclomipramine	Antidepressant	11 ± 2	0.60 ± 0.14
Amodiaquine	Antimalarial	11 ± 3	0.74 ± 0.07
Nortriptyline	Antidepressant	7.5 ± 0.7	0.85 ± 0.46
Maprotiline	Antidepressant	6.6 ± 2.0	1.4 ± 0.3
Quetiapine	Antipsychotic	6.0 ± 0.0	1.4 ± 0.6
Promazine	Antipsychotic	13 ± 0	1.6 ± 0.5
Loperamide	Antidiarrheal	20 ± 4	10 ± 6
Erythromycin	Antibacterial	16 ± 2	15 ± 6
Ondansetron	Anti-emetic	5.9 ± 3.1	2.1 ± 0.8
Tamoxifen	Anti-estrogen	8.9 ± 4.5	2.2 ± 1.5
Loxapine	Anxiolytic	12 ± 5	2.3 ± 0.8
Propafenone	Anti-arrhythmic	20 ± 9	2.5 ± 1.0
Domperidone	Anti-emetic	10 ± 5	3.0 ± 1.4
Cyclobenzaprine	Muscle relaxant	19 ± 4	3.1 ± 1.2
Quinacrine	Anthelmintic/antimalarial	16 ± 6	3.3 ± 0.3
Verapamil	Anti-anginal/anti-arrhythmic	16 ± 4	3.5 ± 1.5
Ketoconazole	Antifungal	19 ± 8	3.5 ± 1.6
Metoclopramide	Anti-emetic	14 ± 10	31 ± 1
Clozapine	Antipsychotic	18 ± 2	4.4 ± 1.8
Tacrine	Cognitive enhancer	8.0 ± 4.5	5.0 ± 3.8
Amlodipine	Antihypertensive/anti-anginal	12 ± 6	5.5 ± 1.9
Olanzapine	Antipsychotic	13 ± 7	6.0 ± 2.0
Salmeterol	Bronchodilator	11 ± 2	9.9 ± 6.8

AO, aldehyde oxidase; IC_{50}, half-maximal inhibitory concentration.

CONCLUSION

Favipiravir provides a substitute for compassionate use in COVID-19 based on its mechanism of action inhibiting virus RdRp and safety data in previous clinical studies. Data obtained from influenza treatment and proof-of-concept clinical trial in EVD aids the determination of dose regimen in clinical trials or experimental use of the drug in COVID-19. However, the exact efficacy of favipiravir awaits further clinical confirmation. Potential DDIs due to AO inhibition should not be ignored in the clinical setting.

SEARCH STRATEGY AND SELECTION CRITERIA

References have been searched using the PubMed database with the key words "Favipiravir" or "T705" and "Pharmacokinetics" or "Clinical trials." Information about the clinical trials for COVID-19 was searched in the ClinicalTrials.gov website

(http://www.chictr.org.cn/searchproj.aspx) using key words "COVID-19," "2019-nCoV," or "2019 novel coronavirus," or "Favipiravir," or "T705."

FUNDING

This work was supported by the National Key R&D Program of China (No. 2017YFC0909302) and the National Natural Science Foundation of China (No. 81673518).

CONFLICT OF INTEREST

Both authors declared no competing interests for this work.

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