



Commentary

Understanding the pharmacokinetics of Favipiravir: Implications for treatment of influenza and COVID-19

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Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an orally bioavailable nucleoside analog that selectively inhibits the PB1 subunit of the RNA-dependent RNA polymerases of influenza with activity against a range of other RNA viruses [1]. Favipiravir has been studied in humans initially for influenza and subsequently for emerging pathogens, including Ebola and COVID-19.

For Ebola, high doses of favipiravir was utilized (day 0: 6000 mg; day 1 to day 9: 2400 mg/d) in an open-label observational study [2]. The dosing was selected to result in target time-weighted average plasma concentration ($C_{ave,u}$) to be 52 $\mu\text{g/ml}$. While therapy was generally well tolerated, mortality was not different from patients who received similar standard of care alone. Unfortunately, despite the high doses, favipiravir concentrations did not result in steady state accumulations (day 2: 46.1 $\mu\text{g/mL}$ (23–106.9); day 4: 25.9 $\mu\text{g/mL}$ (0–173.2), median (range)) seen with typical first-order elimination drugs. No correlation between plasma concentration and decline in Ebola viral load in plasma or mortality was found.

Given *in vitro* data against SARS-CoV-2 and the ability to dose orally, there has been interest in the use of favipiravir for the treatment of COVID-19. In the first study, 3 arms (1800 mg BID x 2 doses then 800 mg BID (high dose) vs. 1600 mg BID x 2 doses then 600 mg BID (low dose) vs. placebo) were studied in hospitalized COVID-19 patients in Russia. Favipiravir was associated with more rapid clearance of PCR and resolution of fever [3]. In the second open-label study, 89 Japanese patients were randomized to early vs late therapy for asymptomatic or mild COVID-19 using high dose favipiravir. Therapy was not associated with a difference in viral clearance ($n=69$ evaluable patients) or a trend to faster defervescence ($n=30$

evaluable patients) [4]. In the last study, 156 Japanese hospitalized COVID-19 patients were randomized to receive high dose favipiravir vs. placebo. Favipiravir was associated with more rapid alleviation of symptoms and PCR negativity (11.9 vs. 14.7 days) [5]. None of the studies included PK assessments of favipiravir.

Clinical trials of favipiravir in uncomplicated influenza studied doses from 1600 to 1800 mg BID on day 1 then 600mg–800 mg BID on day 2–5 (NCT02026349, NCT02008344) [1]. Both trials showed a significant antiviral effect and more rapid symptom resolution. The drug was well tolerated except for transient asymptomatic elevations in uric acid. These and other data led to the approval of favipiravir in 2014 in Japan for the treatment of novel influenza strains.

The CAP-China Network presents data from an study to define PK and outcomes of favipiravir plus oseltamivir in patients ≥ 18 years of age severely ill (respiratory failure, defined as having a $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg or receiving mechanical ventilation) with PCR-confirmed influenza [6]. In this dose-ranging study, 16 severely ill patients received 1600 mg BID on day 1 and 600 mg BID while 19 received 1800 mg BID on day 1 and 800 mg BID; all patients received oseltamivir 75 mg BID; both drugs were given for a total of 10 days. Sparse trough and/or peak blood sample collection was planned (doses 1, 3, 5, 13, and 19) with patients randomized to have additional blood samples on dose 1, 3, and 20. The authors fit a compartmental model with first-order absorption and clearance, with the latter modified by a linear increase in clearance over time. The authors' selected primary PK endpoint, favipiravir $C_{trough} \geq 20$ mg/L after the second dose, was not achieved in either dosing group. Favipiravir C_{trough} decreased significantly over time in both groups ($p < 0.01$) with no change in oseltamivir concentrations over time. Modeling of available data showed that only 18.8% and 42.1% of patients for low and high dose regimen, respectively, achieved $C_{trough} \geq 20$ mg/L for $>80\%$ of the duration of treatment. There was no association between maintaining $C_{trough} \geq 20$ mg/L on day 3 and a reduction in viral loads. Their simulations suggested that a loading dose of ≥ 3600 mg BID for the first day followed by 2600 mg BID for remaining doses would be needed to achieve a target C_{trough} for the duration of treatment. It is important to note, however, that their model fit was limited by a sparse sampling design and led to shrinkage estimates of 49.2% and 53.4% for the between-subject variation of K_a and V , respectively. With shrinkage numbers that exceed 30%, caution

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should be exercised as the model internal validity exceeds the external predictive capacity (such as with simulations) [7]. Their suggested doses, while within the range of that used in Ebola trials, should be considered with extreme caution in COVID-19 as adverse event profiles are very unclear with this dosing paradigm [8,9].

Results from this study, as well as others, demonstrate a highly complex pharmacokinetic profile [10]. The pharmacokinetic complexities combined with mixed efficacy results suggest more studies are needed to understand dosing patients with favipiravir [8–10]. From studies in acute uncomplicated influenza, higher loading and maintenance doses are needed to maintain target drug levels for patients outside of Japan, raising the possibility of pharmacogenomic differences in drug clearance between populations [10]. Further, most studies have documented favipiravir exposures decrease over time, making dosing a challenge. Favipiravir is a prodrug (T-705), requiring phosphorylation to its active form (705-RTP) in the tissues, and the parent prodrug is metabolized to an inactive oxidative metabolite (T-705M1) via aldehyde oxidase. While the authors could only model data with first-order clearance, others have demonstrated that complex zero-order clearance likely occurs, with a time-dependent function that accounts for decreasing concentrations over time [10]. It is unclear if the decreasing concentrations in the setting of stable dosing are a complex function of mixed enzyme inhibition/induction or drug ‘third-spacing’ in tissues and peripheral blood mononuclear cells [10]. This study, as well as others, has demonstrated a time-dependent increase in the ratio of the inactive metabolite to the prodrug (i.e. T-705M: T-705) [10]. These complex pharmacokinetics and the lack of correlation between T-705 drug concentrations and viral decline will require future study to assess tissue and intracellular concentrations of the active T-705-RTP and to elucidate a clearer pharmacokinetic/pharmacodynamic picture.

While there is a need for orally bioavailable agents for COVID-19 and true pharmacodynamic targets are unknown, achieving target favipiravir levels may be even more challenging because of higher half-maximal effective concentrations (EC_{50} of 9.7 mg/L for SARS-CoV-2 vs. 0.03–0.79 mg/L for influenza A) [8–10]. This study provides more information about favipiravir but also highlights the need for

understanding the pharmacokinetic/pharmacodynamic interface before we can begin optimizing dosing, particularly in patients with severe illness [6].

Declaration of Competing Interest

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