CASE REPORT

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Elevated INR in a COVID-19 patient after concomitant administration of favipiravir and warfarin: A case report

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Abstract

What is known and objective: Favipiravir is a promising treatment candidate for managing coronavirus disease 2019 (COVID-19). Warfarin has many drug interactions, but no interactions with favipiravir have been reported.

Case summary: Our patient was taking warfarin for deep vein thrombosis. The international normalized ratio (INR) was stable (1.65 to 2.0); however, it increased to 4.63 after administering favipiravir. The patient had no other factors justifying this change.

What is new and conclusion: Favipiravir and warfarin might have previously unidentified drug interactions that elevated the INR. Therefore, INR must be closely monitored when they are concomitantly administered in COVID-19 patients.

KEYWORDS
coronavirus disease of 2019 (COVID-19), cytochrome P-450 (CYP), drug-drug interactions (DDIs), favipiravir, international normalized ratio (INR), warfarin

1 | WHAT IS KNOWN AND OBJECTIVE

Favipiravir shows potent in vitro activity against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1] and is reported to be effective for coronavirus disease 2019 (COVID-19).[2,3] Favipiravir is metabolized mainly by aldehyde oxidase and partly by xanthine oxidase,[4] but not by cytochrome P-450 (CYP); therefore, drug-drug interactions (DDIs) are less likely. However, pharmaceutical company data indicate that favipiravir has a potent inhibitory effect on CYP2C8 and may cause DDIs that are not yet reported.[5]

Warfarin, an anticoagulant used in the prevention and treatment of various thrombotic disorders, acts by inhibiting the synthesis of vitamin K-dependent clotting factors.[6] Warfarin has a narrow therapeutic index; a small change in its plasma levels may result in concentration-dependent adverse drug reactions/ therapeutic failure. Therefore, its dose must be tailored for each patient according to the individual response, measured as the INR, and the condition

being treated. Warfarin contains a racemic (1:1) mixture of a pair of optical isomers (S-warfarin and R-warfarin). S-warfarin is metabolized by CYP2C9, and R-warfarin is metabolized by CYP1A2 and CYP3A4.[7] Furthermore, involvement of CYP2C8 in the metabolism of S-warfarin and R-warfarin has been reported.[8] It can be inferred that favipiravir, a CYP2C8 inhibitor, may enhance the effects of warfarin. However, no reports are indicating that favipiravir interacts with warfarin and increases the INR. Here, we report a case of elevated INR in a COVID-19 when favipiravir and warfarin were concomitantly administered.

2 | CASE SUMMARY

The patient was a 76-year-old man initially hospitalized for an intramuscular hematoma treatment in the left thigh. The patient's medical history included abdominal aortic aneurysm, chronic

subdural hematoma, acute aortic dissection, deep vein thrombosis and neurogenic bladder. The medication history included warfarin, distigmine, urapidil, ferrous sodium citrate, magnesium oxide and pregabalin. During hospitalization, the patient underwent a reverse transcriptase polymerase chain reaction assay and tested positive for COVID-19 (day 1), after coming in close contact with an infected patient.

Baseline characteristics before favipiravir initiation are shown in Table 1. Laboratory findings revealed increased serum creatinine, CRP, and D-dimer levels, decreased WBC and platelet counts. He was taking warfarin (2.0 mg/day) for deep vein thrombosis, and his INR was in the range of 1.6–2.0, within the target therapeutic range (1.6–2.6). On day 2, the patient had a fever of 40.8°C, a low blood pressure (73/56 mmHg), a high heart rate (105 beats per minute), a respiratory rate of 22 breaths per minute and a low oxygen saturation (92% with nasal O_2 at 2 L/min). Because the patient's condition suddenly deteriorated, favipiravir was administered (orally at 1800 mg twice daily for the first dose and 800 mg twice daily for 14 days; Figure 1). Furthermore, the following drugs were administered: ciclesonide inhalation (400 μg thrice daily for 14 days), intravenous dexamethasone (6.6 mg once daily for 10 days), intravenous ceftriaxone (1 g once daily), carbocisteine (500 mg thrice daily) and vonoprazan (10 mg once daily).

When favipiravir was initiated on day 2, INR was 1.43, slightly below the therapeutic range. However, on day 5, the INR increased to 3.84; therefore, warfarin was discontinued. Moreover, ceftriaxone was also discontinued because of suspected DDIs, whereas other drugs were continued. Blood data showed no hepatic dysfunction, and there was no change in dietary content or volume. On day

TABLE 1 Baseline patient characteristics (day 1)

Subject		Normal range
Gender	Male	–
Age (years)	76	–
Body weight (kg)	77.6	–
Serum creatinine (mg/dl)	1.43	(0.65–1.07)
Serum albumin (g/dl)	3.0	(4.1–5.1)
WBC (×10^3/μl)	2.7	(3.3–8.6)
CRP (mg/dL)	5.63	(<0.20)
Platelet (×10^3/μl)	65	(158–348)
Total bilirubin (mg/dl)	0.66	(0.4–1.5)
AST (U/L)	24	(13–30)
ALT (U/L)	13	(10–42)
LDH (U/L)	215	(124–222)
INR	1.65	(0.85–1.14)
APTT (seconds)	33.1	(22–37)
D-dimer (μg/ml)	171.82	(<1.0)

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRP, C-reactive protein; LDH, alkaline phosphatase and lactate dehydrogenase; WBC, white blood cell.
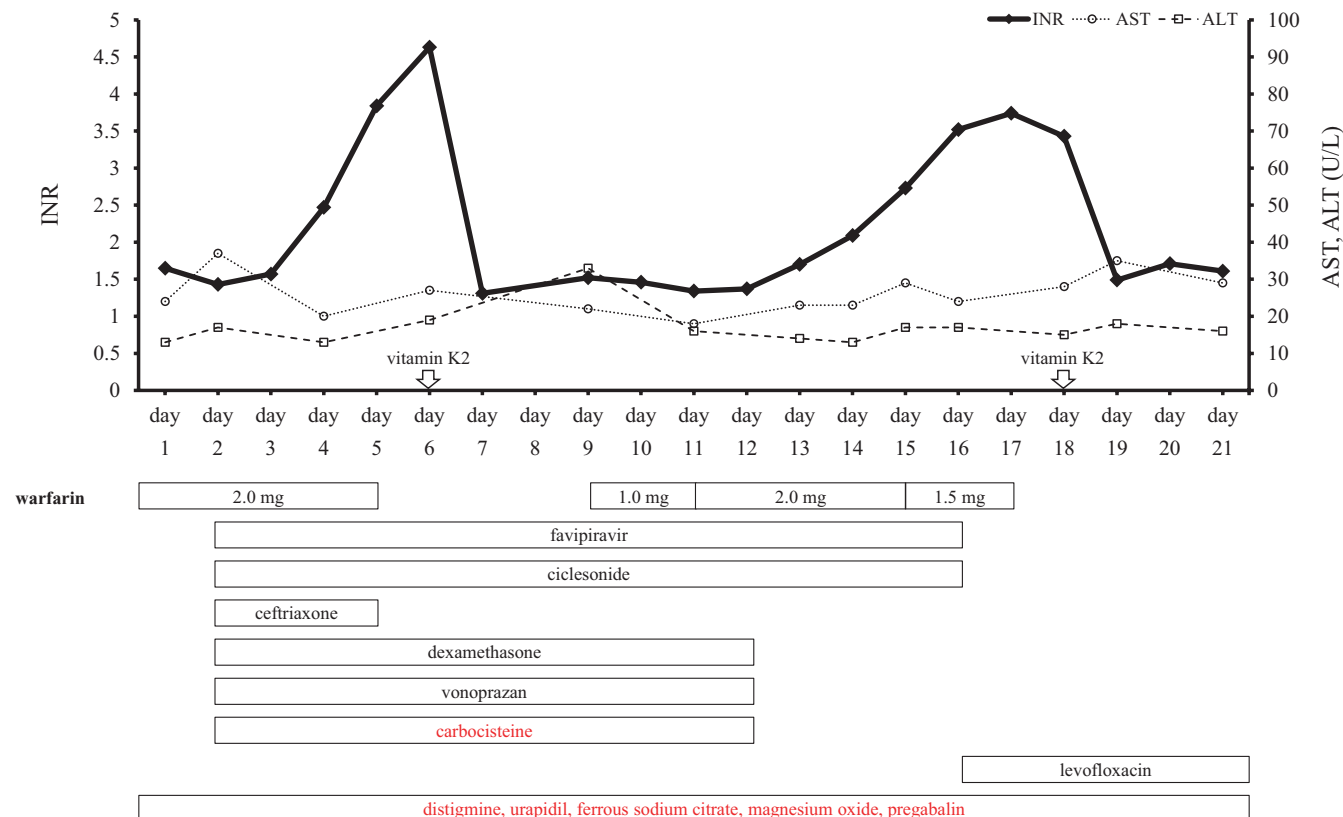
6, the INR further increased to 4.63 despite the discontinuation of warfarin. Vitamin K2 was administered intravenously at 40 mg/day to antagonize the excess anticoagulant action. On day 9, warfarin was restarted at 1.0 mg/day when the INR was 1.52. Warfarin was increased to 2.0 mg/day from day 11. On day 12, dexamethasone and vonoprazan were terminated, and favipiravir and ciclesonide were continued. However, on day 15, the INR increased to 2.73, and warfarin was reduced to 1.5 mg/day, but INR increased to 3.74 by day 17 and was discontinued. Subsequently, vitamin K2 was re-administered at 20 mg/day on day 18, and the patient was switched to another anticoagulant.

COVID-19 can become serious in high-risk individuals, such as the elderly and those with multiple comorbidities.[9] Multiple drug use is inevitable in COVID-19 treatment, especially for patients with comorbidities (hypertension, diabetes and cardiovascular diseases) and COVID-19 complications (such as acute respiratory distress syndrome, shock, arrhythmia and acute kidney injury). Although DDIs must be closely monitored in clinical practice, the information about DDIs caused by new drugs, including favipiravir, is currently limited. This is the first report of elevated INR in a COVID-19 patient when warfarin and favipiravir were administered concomitantly. In this case, the patient's medication adherence was good, and he was taking his medication properly before admission. After admission, he took the same dose of warfarin, and his INR was stable at 1.65–2.0. Therefore, the increase in INR was not due to the patient's hypersensitivity or improving adherence with hospitalization but might have been due to DDIs. INR increased from the second day of starting favipiravir. Factors that affect the INR include diet, liver dysfunction and the concomitant use of drugs.[10] The patient adhered to a warfarin-only diet with limited vitamin K content throughout the hospitalization and had a normal liver function. The regular medications, distigmine, urapidil, ferrous sodium citrate, magnesium oxide and pregabalin, continued. Additionally, COVID-19 alone does not change the INR.[11] From day 2, the patient was treated with multiple drugs, including favipiravir, ceftriaxone, dexamethasone, ciclesonide and vonoprazan. Ceftriaxone, which has been reported to interact with warfarin,[12] was discontinued; however, the INR continued to increase. INR elevation has also been reported when high-dose dexamethasone (>40 mg/day) and warfarin are concomitantly administered.[13] The underlying mechanism for DDIs involves the action of high-dose synthetic glucocorticoids on Niemann-Pick C1-like 1 protein.[14] However, the dose of dexamethasone in this patient was 6.6 mg, which was too low to cause any DDIs. Ciclesonide, an inhaled drug, has a low transferability (<1%) of active metabolites into the blood; therefore, it carries little to no risk of causing DDIs. Although CYP2C19 is inhibited by vonoprazan,[15] no interaction with warfarin has been reported yet. Warfarin was discontinued on day 5 (ie 3 days after favipiravir initiation), but INR increased to 4.63 on day 6, and the patient required vitamin K2 administration. Although warfarin was resumed at half the initial dose (1.0 mg/day) on day 9, the INR increased. Concomitantly, dexamethasone and vonoprazan were discontinued, but favipiravir was not. Thus, warfarin was discontinued twice because of elevated INR, and in both cases,

FIGURE 1 Time course of administration of warfarin and favipiravir and changes in INR and AST/ALT

the only concomitant drug was favipiravir, suggesting DDIs possibility between warfarin and favipiravir. The metabolism of warfarin primarily involves CYP2C9, CYP3A4 and CYP1A2. However, it was recently reported that warfarin is metabolized partly by CYP2C8.[8] CYP2C8 accounts for approximately 6–7% of the total hepatic CYP content[16]; its role in variable drug response through DDIs and pharmacogenetic polymorphisms has been recognized only in the past 10–15 years. Drugs introduced before the role of CYP2C8 was determined may have inadequate or inaccurate product information regarding potential DDIs. In practice, it was initially concluded that montelukast, a leukotriene receptor antagonist, is primarily metabolized by CYP2C9 and CYP3A4.[17] However, in vitro studies conducted more than 10 years later showed that CYP2C8 is a key enzyme involved in the oxidative metabolism of montelukast[18] and that CYP2C8 inhibitors can increase the plasma levels of montelukast.[19] Therefore, it is possible that CYP2C8 inhibitors exhibit DDIs with warfarin as well. The data sheet for favipiravir mentions its concentration-dependent inhibitory effect on CYP2C8, with an IC_{50} value of 74.9 μg/ml. The dose of favipiravir for treating COVID-19 is 1800 mg orally twice daily for the first dose and 800 mg twice daily for a maximum of 14 days. In a phase I study of single-dose favipiravir, the maximum blood concentration was 78.61 μg/ml at 1600 mg and 83.62 μg/ml at 2000 mg.[5] Therefore, it can be inferred that favipiravir reaches the IC_{50} concentration of CYP2C8 at a dose of 1800 mg, and therefore, inhibition of CYP2C8 may occur even at clinical doses. The data sheet states that favipiravir

increases repaglinide blood levels, which CYP2C8 also metabolizes. Therefore, we inferred that the CYP2C8 inhibitory effect of favipiravir partially inhibited the metabolism of warfarin in this case, increasing the blood concentration of warfarin and consequently the INR. The causality of this DDI was also determined using an evaluation scale. The Drug Interaction Probability Scale (DIPS) has been widely used as a criterion for determining adverse events caused by DDI.[20] Using DIPS results, the interaction between favipiravir and warfarin was rated as 'probable', which supported an interaction possibility. Here, favipiravir increased the INR in a patient taking warfarin, and the underlying mechanism may involve its inhibitory effect on CYP2C8. However, the exact mechanism is unknown, as no preliminary studies on the interaction between favipiravir and warfarin have been conducted to date. Therefore, we believe that further research is needed to investigate the interaction possibility between favipiravir and warfarin.

3 | WHAT IS NEW AND CONCLUSION

We present a case in which DDIs between favipiravir and warfarin lead to elevated INR. In COVID-19 patients, the INR should be carefully monitored when these drugs are used concomitantly.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

ETHICAL APPROVAL

This case report was reviewed and approved by the institutional review board of Nihon University Hospital.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying data.

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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