

[CASE REPORT]

Drug Fever Due to Favipiravir Administration for the Treatment of a COVID-19 Patient

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Abstract:

A 55-year-old Japanese man was hospitalized with the novel coronavirus disease 2019 (COVID-19). On the 14th day after the start of favipiravir administration, the patient developed a fever with a temperature of 38.1°C. His pulse rate also became elevated to 128 bpm, so relative bradycardia was not suspected. Since he was in good overall health and no concomitant symptoms and signs were apparent, we considered it to be drug fever due to favipiravir. After the completion of favipiravir treatment, the patient's temperature normalized within 24 hours. We herein report this case of drug fever caused by favipiravir.

Key words: COVID-19, favipiravir, drug fever, hyperuricemia

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Introduction

Favipiravir is an antiviral drug that selectively and potently inhibits the ribonucleic acid (RNA)-dependent RNA polymerase of influenza and many other RNA viruses (1). Favipiravir is administered for 5 days for novel influenza virus infections; however, for the novel coronavirus disease 2019 (COVID-19), a maximum of 14 days has been conducted. Several observational studies of favipiravir use have been conducted to determine its safety and efficacy for COVID-19 treatment (2-4). One case report (5) and one observational study (6) have reported the occurrence of drug fever due to favipiravir administration. In an observational study, fever associated with favipiravir use occurred in 19 of 2,970 cases (0.6%). Therefore, fever is not a rare side effect of favipiravir administration. We herein report a case of drug fever caused by favipiravir administration.

Case Report

A 55-year-old Japanese man experienced a sore throat for

10 days prior to hospital admission. One week prior to admission, he experienced a fever with a temperature of 38.0°C. The patient developed a cough a few days before admission and tested positive for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) via polymerase chain reaction (PCR) on the day before admission. Although the patient did not complain of any shortness of breath, his arterial oxygen saturation was 91% (room air), and concurrent pneumonia was thus identified. He had been prescribed nifedipine (40 mg/day) for hypertension, and he occasionally consumed alcohol. He had no smoking history, and his body mass index was 28.1 kg/m².

Favipiravir treatment was initiated on the evening of day 1, with 3,600 mg divided twice daily on the first day, then 1,600 mg divided twice daily from day 2 onwards. His body temperature normalized on day 4 of favipiravir administration, and he no longer required oxygen therapy by day 11. However, a body temperature of 38.1°C was noted on day 14 (Figure). Acetaminophen (400 mg, single dose) was administered on days 2 and 14.

Physical examination of the head, neck, thoracoabdominal region, and extremities on day 14 revealed no abnormalities.

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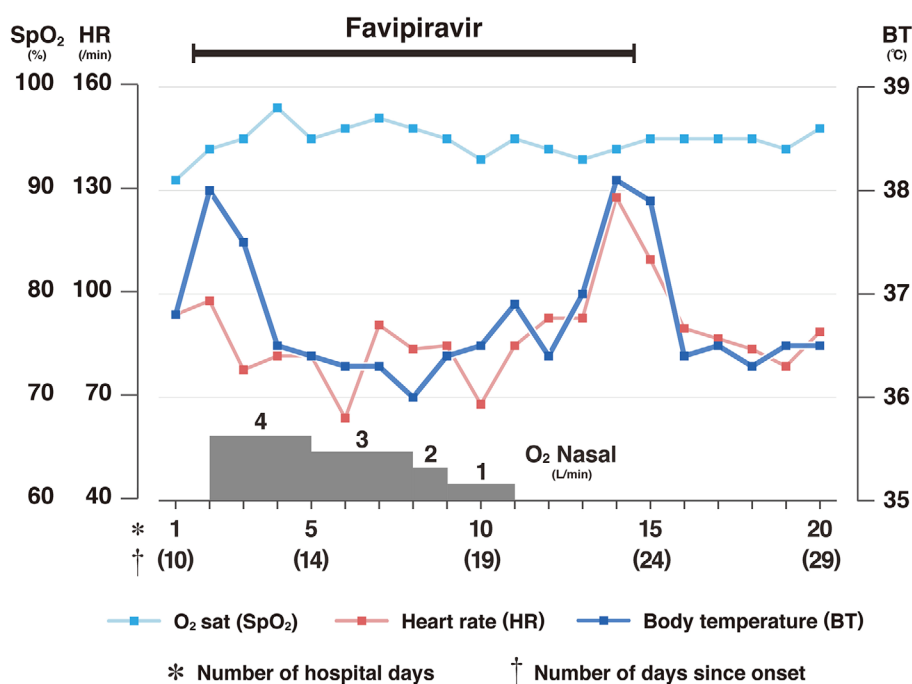


Figure. Changes in body temperature, pulse, and oxygen saturation over the treatment period. Favipiravir was initiated on the evening of day 1. The temperature normalized on day 4 of administration, and the patient no longer required oxygen by day 11. A temperature of 38.1°C was noted on day 14; however, after the discontinuation of favipiravir, the patient's temperature normalized within 24 h. Acetaminophen (400 mg, single dose) was administered on days 2 and 14.

Abnormal findings in blood and serum chemistry tests were noted, including WBC 4,400/ μ L (lymphocytes 21%); alanine aminotransferase, 68 U/L; γ -GTP, 96 U/L; uric acid, 10.9 mg/dL; and C-reactive protein, 0.22 mg/dL. The patient was in good overall health and the fever was not associated with any concomitant respiratory symptoms. After the completion of oral medication, the patient's body temperature normalized within 24 hours. He was subsequently discharged on day 20 after two negative PCR test results.

Discussion

Drug fever, caused by hypersensitivity to a drug or its metabolites, is common; fever often develops from several days to 3 weeks after drug administration. Drugs to which patients have previously been sensitized may cause fever within a few hours of oral administration. The severity varies from asymptomatic mild fever to high fever with chills. Takoi et al. (5) reported that favipiravir-induced drug fever causes relative bradycardia. In general, relative bradycardia is only seen in about 10% of drug fever cases. (7). Our patient did not develop relative bradycardia. Although the favipiravir package insert does not include fever as an adverse event, in this case, the discontinuation of the drug alleviated fever within 24 hours.

Regarding the abnormally high uric acid level, favipiravir-induced hyperuricemia was noted as a warning in the package insert. As such, this finding was also considered to have been caused by the drug. Favipiravir has teratogenicity

warnings and contraindications, and the patient background should be checked prior to its administration. Considering drug side effects, whether previously known or unknown, is important when administering a new drug.

Although all drugs can cause fever due to hypersensitivity, some of the most common causative agents include antiepileptic drugs, antimicrobial drugs, allopurinol, and heparin. Agents known to cause drug fever through other mechanisms include exogenous thyroid hormones, anticholinergic drugs, and drugs affecting the sympathetic nervous system, among others.

In conclusion, it is important to consider drug fever when a patient with good overall health develops fever during hospitalization.

The authors state that they have no Conflict of Interest (COI).

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