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Case Report

Prominent bradycardia in a COVID-19 patient receiving Remdesivir

Sidhi Laksono[1], Grace Trifena Hosea[2]

1) Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Muhammadiyah Prof Dr. Hamka, Indonesia
2) Faculty of Medicine, Universitas Pelita Harapan, Indonesia

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Correspondence:

sidhilaksono@uhamka.ac.id

ABSTRACT

Remdesivir is a commonly used antiviral drug to treat COVID-19. Remdesivir has some side effects; however, whether it has any effect on cardiac is rarely reported. A 44-year-old woman with symptomatic confirmed COVID-19 was treated with intravenous remdesivir 200 mg on day one and followed with 100 mg remdesivir until day five. Three days after the treatment, she had significant bradycardia shown on the electrocardiography; however, the patient had no complaint or symptom regarding the bradycardia. Based on the discussion with the cardiology team, it was decided to cease remdesivir and replace it with oseltamivir, and the ECG showed some improvement. Remdesivir is a drug that should be used safely and cannot be taken at home, as there may be side effects left unaware.

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INTRODUCTION

In this pandemic era of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease (COVID-19), many countries have entered the second wave, including Indonesia. The treatment is given according to the severity of the disease, one of which is antiviral drugs such as remdesivir. Remdesivir is an antiviral commonly used to treat COVID-19 and has some adverse effects. Cardiac adverse events (including supraventricular arrhythmias, atrial fibrillation, and other arrhythmias) are rare in patients treated with this drug. It occurred on 2.6% adverse events in remdesivir administration. Although very few, some have reported that remdesivir also causes bradycardia, a slow or irregular heart rhythm, usually fewer than 60 beats per minute. This case report aims to raise awareness of bradycardia as an adverse event in remdesivir administration (Attena et al., 2021; Hafeez & Grossman, 2021).

CASE REPORT

A 44-year-old woman was referred with confirmed COVID-19. She had been hospitalized two days before. The Computed Tomography scan (CT-scan) showed a normal result. She had a medical history of uncontrolled hypertension. Previously, the patient had received methylprednisolone 4 mg bid, ivermectin protocol, vitamin D od, oseltamivir 75 mg bid, vitamin B and C od, azithromycin 500 mg od, lansoprazole 30 mg od, rivaroxaban 10 mg bid, acetylcysteine bid, and doxycycline 100 mg bid. During the admission, she complained of having fever, cough, and flu, fully alert. The blood pressure was 154/94 mmHg, heart rate 83 bpm, the temperature of 38°C, oxygen saturation of 98%, and other physical examinations were otherwise normal. The chest x-ray showed cardiomegaly and some infiltrate on the left and right lower lobe of the lung, compared to the previous x-ray (**Figure 1**).

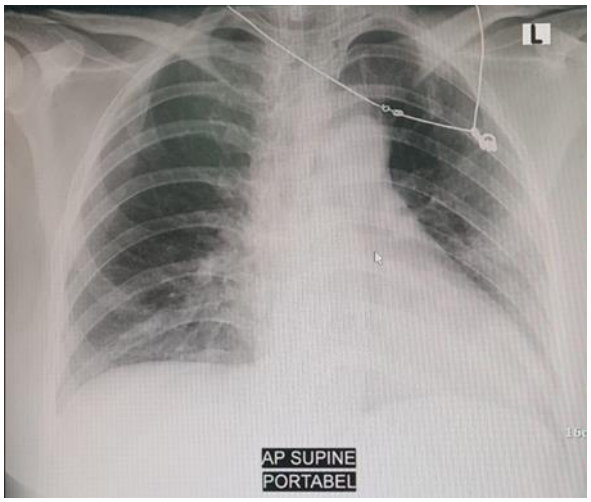

Figure 1. The chest x-ray after admission showed infiltrate on the right and left lower lobe lung

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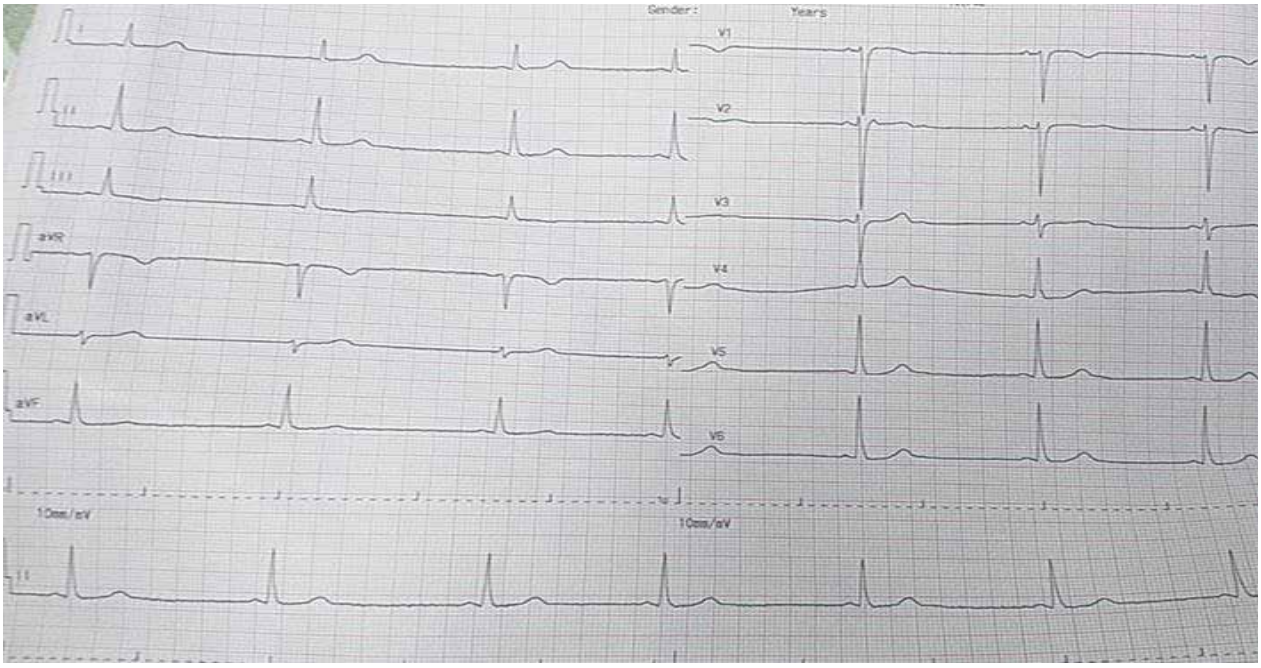

Figure 2. ECG 3 days after receiving remdesivir treatment

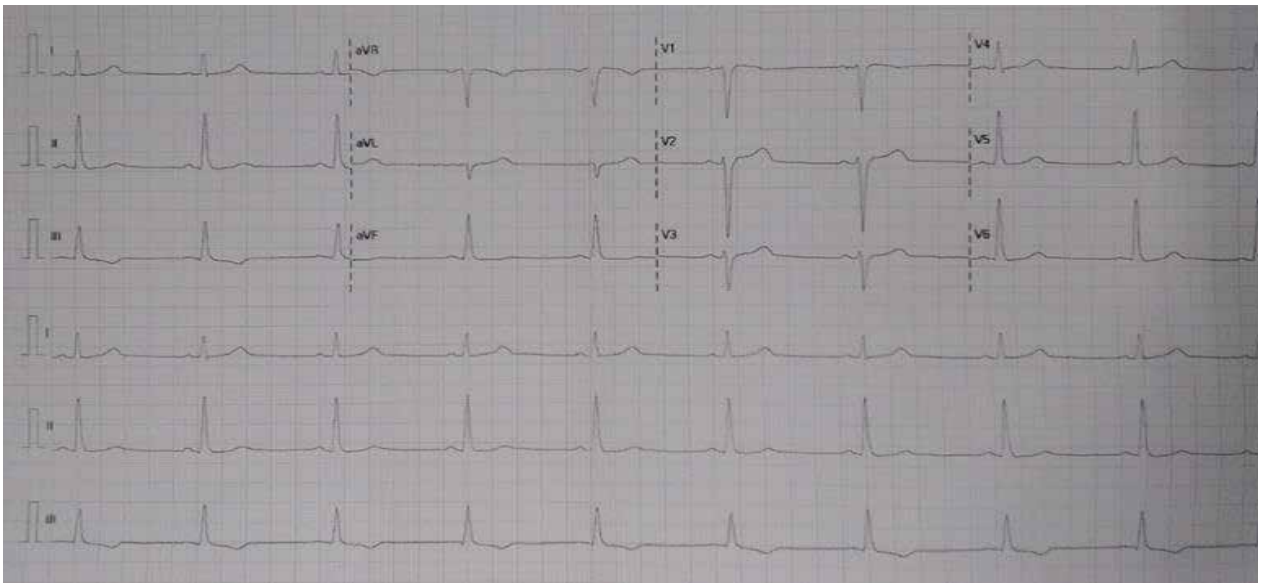

Figure 3. ECG after remdesivir was stopped

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Laboratory investigations were significant for the following: leukopenia (4.72 x 103 UL), lymphopenia (18%), monocytosis (11%), and slightly increased D-dimer (0,61 mg/L). Then the patients started the following treatment: intravenous loading dose remdesivir 200 mg on day one and intravenous remdesivir 100 mg on day two to day five, subcutaneous enoxaparin 2.5 mg, oral ivermectin 24 mg, and oral doxycycline 100 mg. On day 3 of the treatment, the ECG showed bradyarrhythmia with a heart rate of approximately 40 bpm and PR interval of 0,12 s (shown in **Figure 2**); the patient was in a stable condition (no symptoms related to bradycardia). High sensitivity troponin T (hs-TropT) was within normal limits (6.88 ng/L). Based on a discussion with the pulmonologist and cardiologist, we decided to stop Remdesivir, and the ECG showed an improvement in the heart rate of 56 bpm (**Figure 3**). Oseltamivir was given the following day.

DISCUSSION

The patient had already been hospitalized at another hospital for two days. On admission, there were no remarkable physical or examination findings except for her chest x-ray showing an infiltrate on both lungs' lower lobe compared to her previous CT scan. A normal hs-TropT rules out acute myocardial infarction. The patient then was started on COVID-19 treatment, and the antiviral of choice was Remdesivir. Remdesivir was the first antiviral drug approved by the Food and Drug Administration (FDA) for COVID-19 treatment. It was a nucleotide prodrug developed on the early Ebola epidemic in 2013. (Brown et al., 2019; Commissioner, 2020). Remdesivir is indicated for adults and children at least 12-year-old with COVID-19 that are hospitalized with a body weight not less than 40 kg (Commissioner, 2020). As bradycardia occurred in this patient, remdesivir, a guideline-recommended antiviral drug, has to be stopped and substituted with other drugs.

The reported remdesivir side effects were gastrointestinal symptoms, hepatotoxicity, and nephrotoxicity (Fan et al., 2020). In studies done on 53 patients receiving remdesivir, 32 reported increased hepatic enzyme, diarrhea, rash, renal impairment, and hypotension. Those side effects are commonly found in those on mechanical ventilation (Grein et al., 2020). Very few studies reported cardiac side effects. Those cardiac side effects are hypertension, atrial fibrillations, and cardiac arrest, which are not confirmed in a placebo-controlled trial (Grein et al., 2020; Wang et al., 2020). Some case reports describe patients with COVID-19 receiving remdesivir developed bradycardia within three days like the patient in this case (Day et al., 2021; Gubitosa et al., 2020; Gupta et al., 2020; Sanchez-Codez et al., 2021). Another medication known that can cause bradycardia in this patient is enoxaparin, although exceedingly rare (Alquwaizani et al., 2013). The patient did not have comorbidities other than uncontrolled hypertension that can cause sudden bradycardia. Enoxaparin causing bradycardia can be excluded because after the remdesivir was stopped, the patient's heartbeat improved, so it can be said that remdesivir is the cause of the patient's bradycardia.

Some of the most extensive randomized controlled trials (RCT) about remdesivir on COVID-19 are Adaptive COVID-19 Treatment Trial (ACTT-1) and Solidarity Trials by World Health Organization (WHO), has shown varying results. The ACTT-1 compares placebo with remdesivir on hospitalized patients. No significant benefit is demonstrated in patients with mild to moderate disease with a respiratory rate of more than 24x/min or oxygen saturation of more than 94% or without oxygen supplementation. However, the patients receiving remdesivir show faster improvement than the placebo group (Beigel et al., 2020).

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The solidarity trials suggest that the mortality rate is similar to those on standard care (WHO Solidarity Trial Consortium, 2021). According to WHO guidelines, they no longer recommend Remdesivir as COVID-19 treatment, and the National Institute of Health (NIH) COVID-19 treatment guideline also recommends giving remdesivir to the hospitalized patient in need of oxygen supplementation (National Institutes of Health, 2021; World Health Organization, 2020).

The mechanisms for cardiac adverse effects with remdesivir are still limited. The possible mechanisms are that remdesivir active metabolite is similar to adenosine triphosphate, which can reduce sinus node automaticity through vagal stimulation and sinus bradycardia (Pelleg & Belhassen, 2010). Remdesivir has a markedly high binding affinity for viral polymerases; cross-reactivity with human mitochondrial RNA polymerase could lead to mitochondrial dysfunction due to drug-induced cardiotoxicity (Gupta et al., 2020; Sanchez-Codez et al., 2021). Choi and colleagues showed that the cytotoxic effects of remdesivir on cardiomyocytes increased over time, such that a longer duration of treatment (48 h compared to 24 h) was associated with reduced cell viability. Also, Remdesivir, as an adenosine analog, could affect atrioventricular nodal conduction, which could explain the QRS prolongation. (Gubitosa et al., 2020; Gupta et al., 2020; Sanchez-Codez et al., 2021)

In our patient, the bradycardia occurred on day 3 after starting the medication and improved within 24 hours of discontinuing it. She was on no other medications that would otherwise account for the bradyarrhythmia seen, and there were no clinical features suggestive of increased−vagal tone. Although case reports cannot establish causality, this time course raises suspicion that remdesivir was a causative factor. Additionally, although bradycardia has been reported on a few patients with severe COVID-19, our patient did not present with severe COVID-19 and bradycardia before, and the bradycardia occurred after starting remdesivir when he was improving clinically. This case is aligned with the study by Brunetti et al., where the result of a multivariate analysis includes age, gender, cardiovascular risk factors, presence of ischemic heart disease, atrial fibrillation, baseline heart rate, troponin, renal function values, cardiovascular therapy (beta-blockers, amiodarone), and need for ventilation, showed that the only factor significantly related to lower heart rate levels observed after remdesivir administration was a less severe clinical presentation of COVID-19 (Brunetti et al., 2021). This study also aligned with Attena et al.'s study, where the univariable regression for the male sex (relative risk, 0.28 [95% CI, 0.85–0.93]; P=0.038) was associated with a reduced risk of incident sinus bradycardia (Attena et al., 2021). Findings regarding risk factors of bradycardia after administration of remdesivir in COVID-19 patients remain inconsistent. Better evidence is needed to conclude risk factors of bradycardia in COVID-19 patients receiving remdesivir.

CONCLUSION

Remdesivir is a drug often used for COVID-19 treatment, and some cases have already reported its adverse cardiac effect, one of which is bradycardia. This case report was also added to the literature as evidence. The patient, in this case, did not have any medical comorbidities and was not on any medication that could cause bradycardia. The bradycardia improves once Remdesivir is stopped; it suggests that remdesivir is the cause. Patients with less severe COVID-19 symptoms receiving remdesivir should be monitored carefully as there may be missed side effects, so it should never be taken at home. In a patient with less severe COVID-19 symptoms, other antiviral must be considered to be given instead.

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