Journal of the Pediatric Infectious Diseases Society

CASE REPORT

Sinus Bradycardia in a Pediatric Patient Treated With Remdesivir for Acute Coronavirus Disease 2019: A Case Report and a Review of the Literature

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Remdesivir is an RNA polymerase inhibitor that is commonly used in the treatment of patients with severe acute coronavirus disease 2019 (COVID-19). As the severe acute respiratory syndrome coronavirus 2 spreads, the use of remdesivir is likely to increase. Most of the patients treated with remdesivir will not experience any adverse events although some side effects have been reported. Here, we describe a case of sinus bradycardia associated with remdesivir therapy in a pediatric patient with severe acute COVID-19.

Key words. bradycardia; COVID-19; pediatrics; remdesivir; SARS-CoV-2.

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in substantial morbidity and mortality. While there have been fewer cases of COVID-19 in the pediatric population, all age groups are at risk for severe disease. The US Food and Drug Administration approved remdesivir, the first antiviral drug to be used in the treatment of COVID-19, for patients 12 years of age and older. Those less than 12 years of age have access under emergency use authorization. The National Institutes of Health (NIH) COVID-19 treatment guidelines recommend the use of remdesivir in patients who are hospitalized and require supplemental oxygen. The Pediatric Infectious Disease Society's guidance recommends remdesivir for pediatric patients with severe COVID-19, while recognizing that the disease is usually less severe in children; therefore, the benefit is less certain. Generally, remdesivir has been well tolerated, but side effects have been reported. Sinus bradycardia associated with remdesivir treatment has been increasingly reported in pediatric and adult patients. We present a case of acute COVID-19 in a 16-year-old boy who developed sinus bradycardia after the initiation of remdesivir and recovered after discontinuation of therapy.

Received 20 January 2021; editorial decision 13 April 2021; accepted 14 April 2021; Published online June 26, 2021.

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Journal of the Pediatric Infectious Diseases Society 2021;XX(XX):1–4

DOI: 10.1093/jpids/piab029

CASE REPORT

A 16-year-old boy with obesity (body-mass index of 43.9 kg/m^2) and no other past medical history presented to the hospital with respiratory distress. His symptoms started 6 days prior to admission with fatigue and progressed to include headache, dry cough with shortness of breath, and subjective fevers. He also reported several bouts of non-bloody, non-bilious emesis and occasional episodes of non-bloody diarrhea without abdominal pain. Given that he had trouble drinking fluids, he came to the emergency room on day 4 of illness. There, he was afebrile with recorded heart rates between 74 and 92 beats per minute (bpm), respiratory rate 18 breaths per minute, blood pressure 106/51 mmHg with oxygen saturation 99% to 100% in room air. His mother disclosed that she and the patient's sister had both tested positive for SARS-CoV-2 two weeks prior to the patient's symptom onset. His subsequent SARS-CoV-2 by polymerase chain reaction nasopharyngeal swab was positive. He had a white blood cell (WBC) count of 4.7 K/mm^3 with 65.8% neutrophils and 28.5% lymphocytes. He was observed for 8 hours, and given his mild symptoms, he was discharged home.

Over the next 2 days, he developed a worsening cough and difficulty breathing, ultimately returning to the emergency room for assessment. He described chest tightness without chest pain. He also continued to experience nausea, vomiting, and diarrhea. In the emergency room, he was again afebrile but was tachypneic at 32 breaths per minute and his oxygen saturations were 93% to 95% in room air. He was notably tachycardic—ranging from 96 to 110 bpm—although his blood pressure remained stable at 103/63 mmHg. His laboratory results were remarkable for an increase in his WBC to 11.2 K/mm^3 (normal 4.5-11.0 K/mm^3) with 80.8% neutrophils and 5.1%

lymphocytes. He had an erythrocyte sedimentation rate (ESR) of 41 mm/h (normal 0-15 mm/h), a negative SARS-CoV-2 IgG, and a urinalysis without pyuria. A chest x-ray revealed multifocal patchy airspace opacities. Other notable labs included elevated levels of C-reactive protein (CRP) at 24.4 mg/dL (normal ≤0.8 mg/dL), lactate dehydrogenase (LDH) at 1192 IU/L (normal 313-618 IU/L), ferritin at 346 ng/mL (16-107 ng/mL), and fibrinogen at 596 mg/dL (230-450 mg/dL) with a borderline elevated D-dimer at 0.5 mcg/mL (≤0.5 mcg/mL). His remaining laboratory values were normal, including B-type natriuretic peptide (BNP) of 6 pg/mL (normal 0-41 pg/mL), albumin level of 4.1 g/dL (normal 3.8-5.4 g/dL), troponin-I < 0.05 ng/mL (normal <0.05 ng/mL), and alanine transaminase (ALT) of 39 IU/L (normal 5-52 IU/L).

Eight hours after presentation, he was started on 0.5 L/min of supplemental oxygen by nasal cannula to maintain oxygen saturation > 90%. On hospital day 2, Infectious Disease was consulted and, given his clinical picture of severe acute COVID-19, recommended treatment with remdesivir with a plan for 5 days of therapy. It was decided that although he required supplemental oxygen, his hypoxia was mild and he was stable without worsening; therefore, he did not warrant treatment with steroids. Prior to the administration of remdesivir, the patient's heart rate had remained > 90 bpm. His first dose of 200 mg of remdesivir was administered intravenously over 1 hour. His heart rate trended downward over the next 6 hours with the lowest recorded rate at 46 bpm (Figure 1). Over the next 12 hours, his heart rate remained between 48 and 65 bpm with occasional rates up to the mid-70s bpm, despite persistent tachypnea respiratory rate 30–40 breaths per minute and mild hypoxia. He was afebrile throughout the hospital stay. His blood pressure remained stable and he did not require any additional oxygen support beyond the 0.5 L. On hospital day 3, his WBC count, CRP, and LDH decreased to 4.8 K/mm^3 (53% lymphocytes), 14.8 mg/dL, and 980 IU/L, respectively, while his other laboratory values increased, including ESR 48 mm/h, BNP 90 pg/mL, and ALT 59 IU/L. He had a transthoracic echocardiogram due to concern for hyperinflammation or multisystem inflammatory syndrome in children (MIS-C) that showed a normal left ventricular size and systolic function with an ejection fraction of 67%. He had normal coronary arteries without pericardial effusion or valvular dysfunction. Given the overall picture, including positive viral polymerase chain reaction, negative SARS-CoV-2 IgG, and absence of MIS-C symptoms including fever, abdominal pain, rash, or conjunctivitis, it was thought that acute COVID-19 rather than MIS-C was likely the primary process. A 15 lead electrocardiogram (EKG) (Figure 2A) was notable only for sinus bradycardia. Given the concern for remdesivir-induced persistent bradycardia, no further doses of remdesivir were given. From hospital day 3 to 4, his heart rate remained in the range of 40–60 bpm. In the week after discharge, the patient had returned to his usual state of health, and a follow-up EKG 14 days after discharge showed normal sinus rhythm at a heart rate of 107 bpm (Figure 2B). This pediatric patient's case highlights reversible sinus bradycardia as a potential side effect of remdesivir.

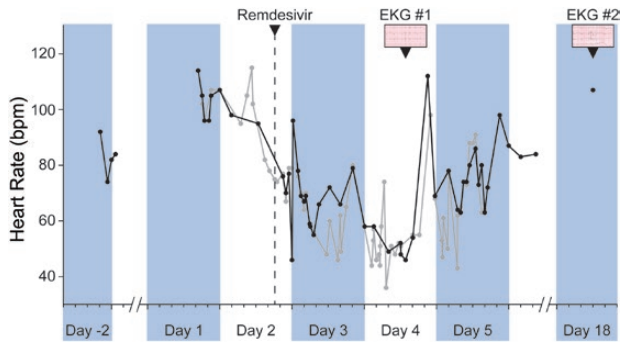

Figure 1. Patient heart rate measured via direct pulse (black) or extracted from the cardiovascular monitor (gray) from the time of initial emergency department presentation (day –2) through hospitalization and including post-discharge follow-up (day 18). Within 12 hours of a single intravenous dose of remdesivir (200 mg), the patient developed progressive bradycardia without hemodynamic compromise that resolved after approximately 60 hours.

DISCUSSION

Since 2020, the appearance and subsequent spread of SARS-CoV-2 have led to widespread interest in identifying antiviral therapies that could be used in treating COVID-19. Remdesivir (GS-5734), a nucleoside analog and an RNA polymerase inhibitor with activity against a range of viruses including coronaviruses, was among the first antiviral therapies used in acute COVID-19. Although early clinical studies have yielded mixed results regarding efficacy, remdesivir is currently one of the few therapeutic options for patients with severe COVID-19, and its widespread use will likely continue as the number of SARS-CoV-2 cases rises. Clinicians should be aware of the potential side effects of the medication.

The safety and effectiveness of remdesivir treatment in pediatric patients <12 years or weighing <40 kg have not been thoroughly assessed. While no deaths were attributed to treatment assignment in clinical trials [1], adverse events were reported, including hepatic enzyme increases, diarrhea, rash, renal dysfunction, hypokalemia, nausea and headache, and atrial fibrillation. Whether all these findings are attributable to remdesivir is not known. The pharmaceutical company drug monograph warns against hypersensitivity reactions and gastrointestinal-related effects [2]. Among the common adverse reactions attributed to remdesivir are nausea and transaminase increases [2]. Guidelines suggest that in cases of increased ALT to >10 times the upper limit of normal, clinicians should consider discontinuation. The NIH treatment guidelines also recommend

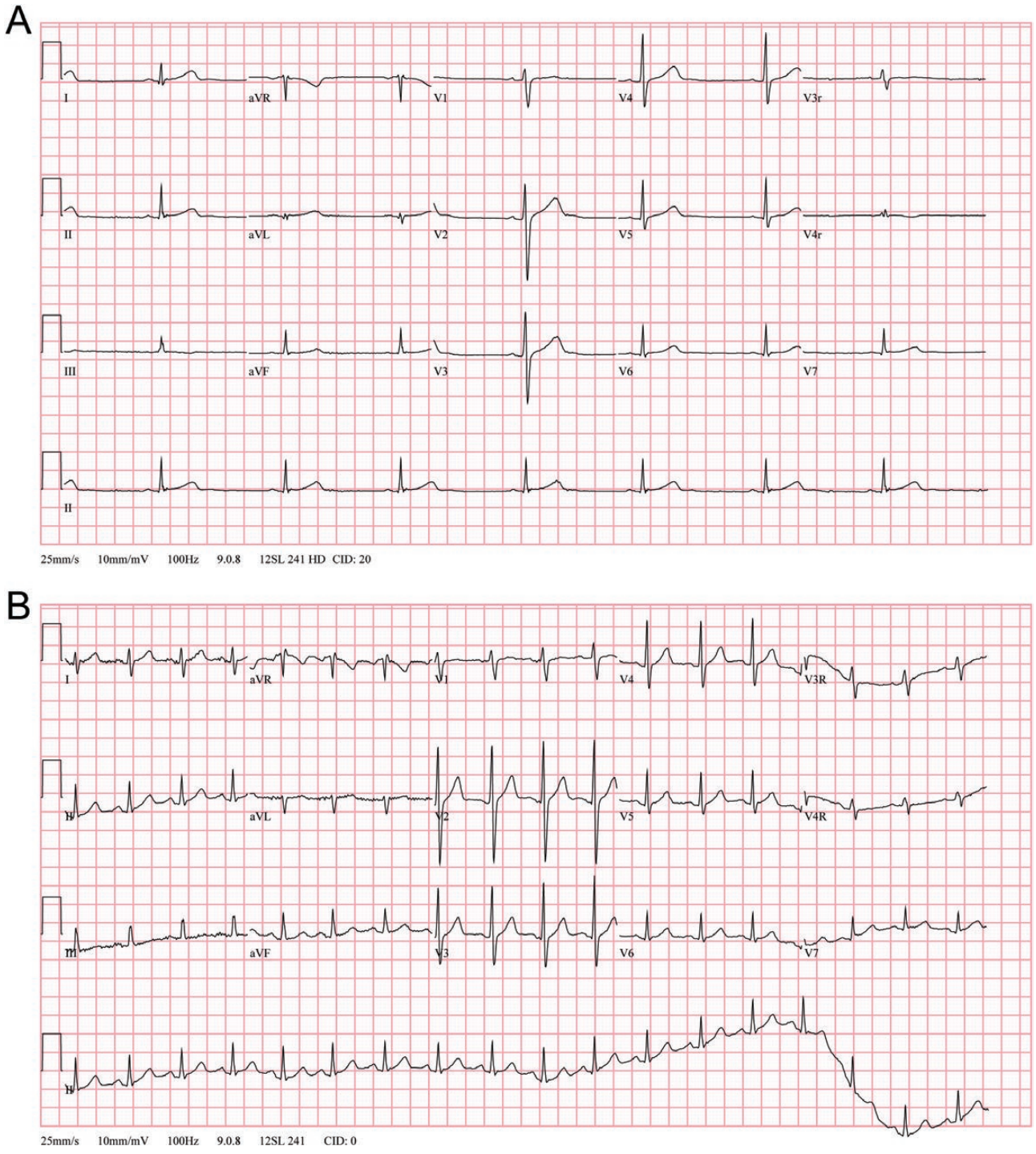

Figure 2. (A) EKG obtained on hospital day 4, approximately 44 hours after the initiation of remdesivir, demonstrating marked sinus bradycardia. (B) Follow-up EKG obtained 12 days after discharge demonstrating the return of normal sinus rhythm.

against its use in patients with renal dysfunction (estimated glomerular filtration rate <30 mL/min) as the remdesivir formulation may contain a renally cleared excipient.

Cardiovascular events associated with remdesivir use are uncommonly reported in clinical trials. However, reports of arrythmias, specifically bradycardia attributed to remdesivir use, have been published in cases of COVID-19. A post-marketing study found that patients who received remdesivir had a 1.7 increased odds of developing bradycardia than those treated with other COVID-19 therapies [3]. One case has been described in a 13-year-old boy with acute COVID-19 who developed asymptomatic sinus bradycardia after the third dose

of remdesivir. Similar to our patient, the bradycardia resolved soon after therapy cessation [4]. Other than asthma, the patient had no other underlying medical conditions. Case reports have also been reported in adult patients including 1 adult patient aged 36 years who developed sinus bradycardia with heart rates to 39 bpm and evaluation finding no secondary causes of low heart rates [5]. In another report of 2 adult patients aged 26 and 77 years, both patients developed sinus bradycardia after 3 days of remdesivir treatment but subsequently improved 3 days after discontinuation of treatment [6]. The 26-year-old patient also developed QTc prolongation, which also resolved. In a separate case report of a 54-year-old woman with a previous history of a left bundle branch block, the patient developed symptomatic sinus bradycardia to 34 bpm after remdesivir administration, which resolved with its discontinuation [7]. The authors proposed remdesivir-induced mitochondrial dysfunction as a mechanism of cardiotoxicity [7, 8]. Another possible mechanism is the close structural relatedness of remdesivir to adenosine, which can cause heart block at the atrioventricular node [7]. Interestingly, our patient rapidly developed bradycardia, which persisted for approximately 60 hours, a time course that closely mimics the published half-life of a nucleoside metabolite of remdesivir [1] and suggests a direct cardiac effect. Other possible explanations include drug-drug interactions, exacerbation of underlying cardiovascular disease, and multifactorial effects from underlying inflammation and SARS-CoV-2 electrolyte derangements. Viral-induced relative bradycardia has been described but is generally less profound than that described here. Our patient had no underlying medical conditions other than obesity, and while he had signs and symptoms of severe COVID-19, his respiratory symptoms did not worsen over the time he developed bradycardia.

We report a pediatric case of severe acute COVID-19 who developed sinus bradycardia after initial loading dose of remdesivir. Two days after remdesivir was discontinued, his heart rate improved back to his baseline. While severe COVID-19 is less common in pediatric patients, the continued spread of SARS-CoV-2 will lead to increased pediatric cases and will likely increase the use of remdesivir. Clinicians, including pediatricians, should be aware of this potential cardiovascular effect of remdesivir administration.

Notes

Financial support. C. S. is supported by National Institute of Allergy and Infectious Diseases (grant number K08AI150996-01).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 – final report. N Engl J Med **2020**; 383:1813–26.
2. Highlights of Prescribing Information: Veklury (remdesivir). Accessed December 20, 2020. https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf
3. Touafchia A, Bagheri H, Carrie D, et al. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns. Clin Microbiol Infect **2021**; 27:791.e5–791.e8.
4. Sanchez-Codez MI, Rodriguez-Gonzalez M, Gutierrez-Rosa I. Severe sinus bradycardia associated with remdesivir in a child with severe SARS-CoV-2 infection. Eur J Pediatr **2021**;180:1627.
5. Barkas F, Styla CP, Bechlioulis A, Milionis H, Liberopoulos E. Sinus bradycardia associated with remdesivir treatment in COVID-19: a case report and literature review. J Cardiovasc Dev Dis **2021**; 8:18.
6. Gupta AK, Parker BM, Priyadarshi V, Parker J. Cardiac adverse events with remdesivir in COVID-19 infection. Cureus **2020**; 12:e11132.
7. Gubitosa JC, Kakar P, Gerula C, et al. Marked sinus bradycardia associated with remdesivir in COVID-19: a case and literature review. JACC Case Rep **2020**; 2:2260–4.
8. Varga ZV, Ferdinandy P, Liaudet L, Pacher P. Drug-induced mitochondrial dysfunction and cardiotoxicity. Am J Physiol Heart Circ Physiol **2015**; 309:H1453–67.