Remdesivir-associated bradycardia

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SUMMARY
Remdesivir is an antiviral used for the treatment of COVID-19 requiring hospitalisation. Information on its cardiovascular safety profile is scarce. We report the case of a 37-year-old man with COVID-19 who developed bradycardia after receiving remdesivir. We recommend a baseline ECG for all patients prior to receiving remdesivir and continuous cardiac monitoring during treatment, especially among those with underlying cardiovascular disease, elderly and using β-blockers.

BACKGROUND
As of June 2021, 178 million cases of COVID-19 have been confirmed, including 3.9 million deaths worldwide. Remdesivir is an antiviral that was approved by the US Federal Drug Administration through emergency use authorisation for use in adult and paediatric patients with severe COVID-19. Not shown to confer mortality benefit, it is given to these patients as it shortens the time to recovery among those who require supplemental oxygen, but not intubated.1 Despite remdesivir’s wide use, not much is known about its cardiovascular safety profile. We hereby report a case of a patient with COVID-19 who developed bradycardia after receiving remdesivir.

CASE PRESENTATION
A 37-year-old man with hypertension presented with 7-day dyspnoea. He had fever, cough, malaise, anosmia and hypogeusia.Valsartan was his only medication. He did not smoke cigarettes, take alcohol or illicit drugs. He had not recently travelled. On presentation, he was normotensive (blood pressure 118/71 mm Hg), but tachycardic (heart rate 102 beats/min), tachypnoeic (respiratory rate 33 breaths/min) and febrile (temperature 38.2°C). Hypoxic, he required supplemental oxygen via nasal cannula. Lungs were clear to auscultation. Heart rhythm was regular and he did not have any murmur.

Complete blood count was normal. Except for hyponatraemia (sodium 132 mmol/L) and acute kidney injury (creatinine 1.5 mg/dL), the results of the chemistry panel were within normal limits. Chest radiograph showed bilateral patchy lung infiltrates. With a positive SARS-CoV-2 test result, he was diagnosed with severe COVID-19 and was started on dexamethasone and remdesivir. Home valsartan was held because of normotension. Kidney function improved with intravenous fluid. A few hours after receiving the second dose of remdesivir on hospital day 2, he developed asymptomatic sinus bradycardia at 40–44 beats/min (figure 1). Transthoracic echocardiogram was unremarkable. Remdesivir was discontinued and heart rate improved.

OUTCOME AND FOLLOW-UP
On hospital day 6, his heart rate increased to 56–58 beats/min and he was discharged home. He continued monitoring himself and reported heart rate normalisation (60–70 beats/min) 2 days after discharge. No recurrence of bradycardia was noted on 2-month follow-up.

DISCUSSION
Remdesivir is a prodrug with broad-spectrum antiviral activity. As a nucleoside analogue, it incorporates itself into the viral RNA and inhibits RNA-dependent RNA polymerase, and consequently, viral replication. Most commonly reported adverse events are gastrointestinal and renal: liver enzyme elevation, nausea, vomiting, constipation, diarrhoea and acute kidney injury.2 Though few cases of hypotension, atrial fibrillation and cardiac arrest have been reported,3 not much is known about its cardiovascular adverse events. As remdesivir is used more, bradycardia is increasingly recognised as an adverse event.4–7 Analysis of WHO pharmacovigilance database showed that 3.6% of 2603 reports for remdesivir were bradycardia.8 Affected individuals were aged 6–90 years with a mean age of 61.2 years (SD 18.1).8 With a median onset of bradycardia of 2.4 days, remdesivir use is associated with 65% increased likelihood of reporting bradycardia compared with use of hydroxychloroquine, lopinavir/ritonavir, tocilizumab or glucocorticoids.9

The mechanism for bradycardia is unknown. A proposed explanation is mitochondrial dysfunction.1 Remdesivir’s triphosphate form is more efficiently incorporated into RNA than ATP.10 Despite its strong affinity for viral RNA polymerase, remdesivir may involve human mitochondrial RNA polymerase, leading to deterioration of mitochondrial function and cardiotoxicity.1 Suppression of cardiac pacemaker is another potential mechanism. ATP has negative chronotropic and dromotropic effects in the heart that are mediated by its metabolite adenosine as well as a cardiodepressive reflex.10 Similar to ATP, remdesivir could also affect the sinoatrial node.
Case report

We recommend a baseline ECG for all patients prior to receiving remdesivir. Our patient’s ECG on admission was sinus rhythm. Cardiac monitoring is essential in remaining vigilant against possible complications of treatment, especially among those with underlying cardiovascular disease, elderly and using β-blockers.

Learning points

- Remdesivir is associated with bradycardia.
- Proposed mechanisms for remdesivir-associated bradycardia include mitochondrial dysfunction and cardiac pacemaker suppression.
- Baseline ECG should be obtained for all patients prior to receiving remdesivir.
- Cardiac monitoring should be done on all patients receiving remdesivir, especially among those with underlying cardiovascular disease, elderly and using β-blockers.

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