



Intention Tremor as an Adverse Effect of Remdesivir Therapy for COVID-19 in an Obstetric Patient

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Abstract

Remdesivir, an inhibitor of viral RNA polymerase, was initially developed as a potential treatment for hepatitis C and subsequently studied in Ebola, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS) outbreaks. Now, the Coronavirus Disease 2019 (COVID-19) pandemic has increased the global utilization of remdesivir as an experimental therapy for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This widespread utilization may lead to the detection of new adverse effects that have not previously been reported. The most common adverse effects associated with remdesivir include nausea, mild elevations in ALT and AST, and acute kidney injury. In this report, we describe the development of an intention tremor as an adverse effect of remdesivir therapy for COVID-19 in an obstetric patient. The tremor resolved after discontinuation of remdesivir and the patient was discharged home after clinical improvement.

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Introduction

At the time of this report, there have been over 23 million cases and 800,000 deaths attributed to COVID-19 worldwide. The discovery and rapid global dissemination of the novel coronavirus SARS-CoV-2 in late 2019 led to the identification of several drugs as potential treatments. Among these was the antiviral drug remdesivir, a nucleoside analog that inhibits viral RNA-dependent RNA polymerase. In addition to investigations into its activity against Hepatitis C and Ebola virus, it has previously been shown to have activity against the SARS coronavirus in vitro and the MERS coronavirus both in vitro and in vivo [1-3].

Studies by Wang et al demonstrated in vitro activity of remdesivir against SARS-CoV-2 [4]. Early clinical data indicated that remdesivir may reduce time to extubation, increase rate of extubation, and decrease mortality in COVID-19 patients requiring mechanical ventilation [5]. Further studies showed that a 5-day course may be sufficient to produce a clinical benefit while decreasing the risk of adverse effects [6].

Due to known toxicities, routine monitoring of hepatic and renal function is expected for patients being treated with remdesivir, and treatment may be stopped if significant organ dysfunction develops. But our current knowledge about the adverse effects of remdesivir is limited, and somewhat obscured by the complex, multi-system manifestations of COVID-19 illness.



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Here we present a case of tremor as an adverse effect of remdesivir treatment for COVID-19 in an obstetric patient. To our knowledge, this adverse effect has not previously been reported in the literature.

Case

A 34-year-old woman (G1P0) at 22 weeks of gestation presented to the emergency department with chief complaint of 1 week of nausea and vomiting, decreased oral intake, and shortness of breath in the context of known COVID-19 infection. She also reported 1 day of cough and a fever at home of 38.2 °C (100.8 °F). Her medical history was significant for type 1 diabetes and chronic hypertension. Home medications included labetalol 600 mg BID and glargine 34 units, Humalog 45U divided at breakfast, lunch, and dinner. The patient had initially been evaluated for shortness of breath in the emergency department 10 days prior, and at that time was afebrile with an oxygen saturation of 98% on room air. A workup for COVID-19 and pulmonary embolism were negative, and she was discharged home. Three days prior to admission she presented to an outside hospital with persistent shortness of breath, where she tested positive for SARS-CoV-2 and began self-isolating at home.

In the emergency department, her vital signs were temperature 38.5 °C (101.3° F), heart rate 99 bpm, blood pressure 140/69 mmHg, and oxygen saturation 95% on room air. Laboratory results were significant for mild hypokalemia and normocytic anemia. She was also found to have ketonuria which improved with IV hydration. Chest X-ray (CXR) showed ill-defined ground glass opacities in the bilateral lower lungs. The patient was started on 500 mg IV azithromycin and 2g IV ceftriaxone for possible superimposed Community Acquired Pneumonia (CAP) and admitted to the antepartum unit.

Her gastrointestinal symptoms improved early in her hospital course, but she developed progressive respiratory failure. For the first 3 days of her hospitalization, she required 2 L/min supplemental oxygen by Nasal Cannula (NC). She was intermittently tachypneic with respiratory rates in the 30s and had subjectively increased work of breathing. She had worsening bilateral pulmonary infiltrates on serial CXRs and laboratory results showed increasing lymphopenia (neutrophil/lymphocyte ratio = 8:1). The patient was not determined to be a candidate for convalescent plasma based on her current O₂ requirements and she did not immediately consent to remdesivir, although she was approved through compassionate use. She was started on a 10-day course of dexamethasone 6 mg IV q24h and her insulin requirements were adjusted accordingly [7]. She was also prescribed subcutaneous heparin at prophylactic dose with a plan to initiate therapeutic dosing if her D-dimer reached ≥ 3.0 . The patient remained on 2-3 L/min NC for the next two days with intermittent spikes in blood pressure to the 160s-180s systolic, which was controlled with IV labetalol, and this was determined with clinical and laboratory data to be an exacerbation of her chronic hypertension rather than pre-eclampsia.

On hospital day 5 the patient developed fever of 38.3 °C (100.9 °F) and worsening respiratory failure, requiring up to 6 L/min NC to maintain oxygen saturation of $\geq 94\%$. She was transferred from the antepartum unit to the COVID ICU. The following day the patient agreed to initiate a 5-day course of remdesivir at 200 mg IV on day 1, followed by 4 days of 100 mg IV daily [6]. On day 2 of remdesivir therapy, she remained stable on 2-3

L/min NC with only mild shortness of breath. That night, her nurse noted an acute onset, 1-3 cm and fast frequency tremor of both hands of which the patient was initially unaware. The tremor worsened over the next 48 hours until it was so severe that the patient struggled to perform her own insulin injections. On physical exam, the tremor was noted to be worsened with activity and diminished at rest. A decision was made to stop remdesivir after 4/5 doses due to the potential association with the tremor and concern that it was exacerbating the patient's chronic hypertension. The tremor resolved within 24h after the last dose of remdesivir. She completed the 10-day course of dexamethasone as planned as well as an antibiotic course for CAP. Over the next 13 days, the patient had waxing and waning oxygen requirements with a maximum of 6 L/min NC, but she was successfully weaned to room air. She was discharged home without supplemental oxygen on hospital day 21 after two negative COVID PCRs, with plans for close follow-up for the duration of her pregnancy.

Discussion

As the pandemic continues, investigations into drug therapies for COVID-19 are ongoing and several promising vaccine candidates are being distributed to community throughout the nation.

The current data is mixed with regard to the most effective therapy and/or prophylaxis for COVID-19, and guidelines continue to change as our knowledge evolves. As we treat novel diseases in novel patient populations, it is important to note any potential complications of medical therapy in order to appropriately weigh the risks and benefits of treatment.

Here we described the development of an intention tremor in an obstetric patient after two doses of remdesivir for the treatment of COVID-19. In this case, the patient's tremor resolved quickly and completely after discontinuation of the drug. We excluded other possible causes of tremor, including hypoglycemia or adrenergic medications. Corticosteroids can enhance physiologic tremor, and our patient was receiving dexamethasone; however, the temporality of onset and resolution of her tremor was more consistent with remdesivir as the etiology.

This patient had multiple risk factors for complications of COVID-19, including a 20-year history of diabetes mellitus and chronic hypertension. Further complicating her case was her pregnancy, which comes with immunologic changes that may put her at higher risk of severe disease.

As pregnant women are often excluded from clinical trials, data on use of remdesivir in obstetric patients is lacking. The only report of remdesivir use in pregnant women prior to the COVID-19 pandemic is a 2019 randomized clinical trial in Ebola patients, where no adverse effects were reported among six pregnant women treated with remdesivir [8].

In the most severe cases, there have been reports of multi organ failure, AKI, hypotension in patients treated with remdesivir for COVID-19; However, these adverse effects may be attributable to the underlying severe COVID-19 illness rather than remdesivir, and it is challenging to make this distinction [9]. SARS-CoV-2 infection is now recognized to cause widespread multi-system dysfunction, including ARDS, hypercoagulability, myocarditis, encephalitis and more [4,5,9]. More clinical trial data is needed to fully characterize the benefits and risks of this drug in the context of COVID-19 treatment.

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