Case Report

Remdesivir-Warfarin Interaction: A Case Report

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Abstract

Description

A greater than 65-year-old Caucasian woman receiving long-term anticoagulation with warfarin for atrial fibrillation experienced a sudden rise in an international normalized ratio (INR) after she was started on remdesivir for management of 2019 Novel Coronavirus (COVID-19). Patient INR was maintained within the target therapeutic range of 2–3 with a warfarin dose of 11 mg/week before starting remdesivir. After 2 days of remdesivir therapy, the patient's INR increased significantly and remained elevated during the 5 day course of remdesivir therapy. Patient required an interruption of her warfarin therapy for 7 days, and her INR did not return to the targeted therapeutic INR range of 2–3 until day 5 from the last dose of remdesivir, despite no warfarin administration. A comprehensive PubMed/MEDLINE search did not find published literature documenting interaction between warfarin and remdesivir. We describe the first case report, to our knowledge, documenting a potential drug interaction between warfarin and remdesivir. The authors found that there is a probable interaction between warfarin and remdesivir when applying the Adverse Drug Reaction Probability Scale, Naranjo Scale. To reduce the risk of bleeding associated with excessive anticoagulation, clinicians should closely monitor INR, and adjust the warfarin dose accordingly when patients are receiving remdesivir and warfarin concomitantly.

Keywords

SARS-CoV-2; COVID-19; coronavirus infections/therapy; warfarin; remdesivir; antiviral agents; drug interactions; drug repositioning

Introduction

Remdesivir (formerly GS-5734) is a monophosphoramidate nucleoside analogue prodrug that has shown broad-spectrum activity against several coronaviruses including SARS-CoV-2, a virus responsible for causing COVID-19.[1] The U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) on May 1st, 2020 to allow emergency use of remdesivir for treatment of hospitalized patients with severe COVID-19.[2-3] There is currently a lack of in vivo data regarding remdesivir drug interactions. In vitro data have shown that remdesivir is an inhibitor of CYP3A4, and a weak inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6.[4] As a prodrug, remdesivir is rapidly converted to its active nucleoside triphosphate form of GS-443902 and other metabolites.[4] The metabolism of remdesivir's metabolites has not been studied and data regarding their interaction with other drugs is lacking. Warfarin, a vitamin K antagonist, is a commonly used anticoagulant for prophylaxis and treatment of venous thrombosis, pulmonary embolism and thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.[5] Warfarin is often used to reduce the risk of death, recurrent myocardial infarction and thromboembolic events such as stroke or systemic embolization after myocardial infarction.[5] Warfarin drug interactions are mainly due to its hepatic metabolism through the cytochrome P450 system by CYP2C9, CYP1A2 and CYP3A4.[6] Although several drug interactions with warfarin are well described in the literature,[7] there is a lack of data regarding interaction between remdesivir and warfarin. We describe the first case report, to our knowledge, documenting a probable drug interaction between remdesivir and warfarin.

Case Presentation

A greater than 65-year-old Caucasian woman was admitted at North Florida Regional Medical Center due to shortness of breath with productive cough. Her relevant medical history included atrial fibrillation, hypertension, and chronic obstructive pulmonary disease (COPD) requiring 4 liters of home oxygen therapy. Her routine medications consisted of warfarin 11 mg/week with stable INR (2 mg oral [PO] on Sunday, Monday, Wednesday and Friday, and 1 mg PO on Tuesday, Thursday and Saturday), ipratropium bromide 17 mcg/act 2 puff inhaled four times a day, fluticasone propionate 50 mcg/act twice daily as needed for nasal congestion, potassium chloride 20 meq PO daily, furosemide 40 mg PO daily, levothyroxine 150 mcg PO daily, cyanocobalamin 1,000 mcg PO daily, cholecalciferol 1,000 units PO daily and simvastatin 40 mg PO at bedtime. The vital signs on admission were Tmax of 37.1°C, blood pressure 141/65 mm Hg, pulse 77 beats per minute, respiratory rate 18 breaths per minute and oxygen saturation of 100% on 10 liters of oxygen via nasal cannula. The chest X-ray on admission showed right lower lobe airspace disease concerning for pneumonia. In addition to the continuation of home medications, the patient was started on ampicillin/sulbactam 1.5 gm IV every 8 hours and doxycycline 100 mg PO every 12 hours for a 5 day course of therapy. A COVID-19 test was collected on admission and the result came back positive. The patient was then started on hydroxychloroquine 400 mg PO every 12 hours for 2 doses, then 400 mg PO every 24 hours for 3 days until patient was switched to remdesivir when it became available under the EUA. Throughout the course of her hospitalization, the INR was stable until the start of remdesivir. (**Table 1**) Despite significant reduction in warfarin dose, the INR remained elevated until the patient finished her treatment course with remdesivir and the INR slowly stabilized again. Other liver function tests remained stable and within normal limits throughout the administration of remdesivir. (**Table 2**)

Discussion

Remdesivir is a novel antiviral currently being used in clinical practice for treatment of hospitalized patients with COVID-19. Remdesivir's mechanism of action is through inhibition of SARS-COV-2 RNA-dependent RNA polymeras-

Table 1. Summary of the Patient's Anticoagulation Management.

Day	INR (Goal 2-3)	Warfarin Dose	Comments
Admission (day 1)	2.3 (admission baseline)	1 mg	Patient started on ampicillin/sulbactam and doxycycline.
Day 2	2.3	2 mg	Hydroxychloroquine started.
Day 3	2.4	2 mg	
Day 4	-	1 mg	Remdesivir 200 mg x1 loading dose started. Hydroxychloroquine stopped.
Day 5	2.5	2 mg	Ampicillin/sulbactam and doxycycline stopped. Remdesivir 100 mg IV daily ordered.
Day 6	3.4	hold	
Day 7	3.8	hold	
Day 8	4.2	hold	Last dose of remdesivir taken.
Day 9	4.6	hold	
Day 10	4.1	hold	
Day 11	3.8	hold	
Day 12	3.2	hold	
Day 13	2.4	1 mg	

Table 2. Liver Function Tests.

Day	Aspartate transaminase (AST) (units/L) Ref. 15-37	Alanine transaminase (ALT) (Units/L) Ref. 13-56	Total bilirubin (mg/dl) Ref. 0.2-1	Direct bilirubin (mg/dl) Ref. 0- 0.2	Comments
Admission (day 1)	13	9	0.4	0.1	
Day 3	15	8	0.5	0.1	1 day prior to starting remdesivir therapy.
Day 6	14	9	0.6	0.2	
Day 7	13	8	0.9	0.2	

Ref. = Reference range

es (RdRps) by incorporating its active nucleoside triphosphate, GS-443902, into the nascent RNA chains.[4] In addition to its active metabolites, remdesivir is rapidly converted to other metabolites, mostly GS-704277 and the nucleoside analog GS-441524, once inside the cell.[4] In vitro studies have shown that remdesivir is an inhibitor of CYP3A4, and a weak inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP2D6.[4] The impact of remdesivir's metabolites on the cytochrome P450 system is unknown.

Warfarin is a commonly used medication in clinical practice for patients requiring long-term anticoagulation. Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors and the anticoagulant proteins C and S. Warfarin exists as a racemic mixture of R-warfarin and S-warfarin isomers. The S-isomer is 5 times more potent than the R-isomer and is metabolized primarily by CYP2C9, whereas the R-isomer is metabolized by CYP1A2 and CYP3A4 isoenzymes.[6,7] Drugs that inhibit CYP2C9, CYP1A2 and/or CYP3A4 can increase INR by increasing exposure to warfarin.[6]

The extent of remdesivir and its metabolites' inhibition of the hepatic cytochrome P450 isoenzymes that metabolize warfarin is not characterized in clinical practice. A comprehensive PubMed/MEDLINE search found no documentation in the literature of warfarin and remdesivir interaction. We report the first case to our knowledge of a potential drug interaction between remdesivir and warfarin.

This case report describes a patient who had a stable INR within the therapeutic range of 2–3 while taking a warfarin dose of 11 mg/week prior to admission. The INR remained stable for the first 5 days of hospitalization, then suddenly increased on the third day of remdesivir therapy. The patient completed a 5-day course of both ampicillin/sulbactam and doxycycline with stable INR results without modification to the patient's home warfarin regimen. The only change that took place before the noted INR elevation was the start of remdesivir 2 days prior. The INR remained elevated for the duration of remdesivir therapy, then began declining upon completion of remdesivir treatment. The INR did not return to the targeted therapeutic range of 2–3 until 5 days after the last dose of remdesivir. All other liver function tests remained within normal limits during the course of remdesivir therapy. The calculated Naranjo scale probability score was 6, suggesting that the noted INR increase was secondary to a probable drug interaction between warfarin and remdesivir. (**Table 3**) The likely explanation of the INR elevation in this patient is decreased clearance of warfarin due to its interaction with remdesivir and/or remdesivir's metabolites through the cytochrome P450 system.

Conclusion

Remdesivir is currently used widely for treatment of COVID-19 patients due to its documented clinical benefits of shortening the time to recovery.[9] The spectrum of remdesivir drug interaction in clinical practice is not well characterized. We report the first case, to our knowledge, documenting a probable drug interaction between warfarin and remdesivir. This case report describes a patient who experienced a significant rise in INR 2 days after remdesivir

Table 3. Adverse Drug Reaction Probability Scale, Naranjo Scale: remdesivir-warfarin interaction.

Adverse Drug Reaction Probability Scale (Yes, No, Do Not Know)	Score
1. Are there previous conclusive reports on this reaction? (+1,0,0)	0
2. Did the adverse event appear after the suspected drug was administered? (+2,-1,0)	2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? (+1,0,0)	1
4. Did the adverse event reappear when the drug was readministered? (+2,-1,0)	0
5. Are there alternative causes that could on their own have caused the reaction? (-1,+2,0)	2
6. Did the reaction reappear when a placebo was given? (-1,+1,0)	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic? (+1,0,0)	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? (+1,0,0)	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? (+1,0,0)	0
10. Was the adverse event confirmed by any objective evidence? (+1,0,0)	1
Total score	6

Total score ≤ 0: Doubtful; Total score 1 to 4: possible; Total score 5 to 8: probable; Total score ≥9: definite

therapy initiation, which required an interruption of warfarin therapy for 7 days. Clinicians should closely monitor INR in patients who are on warfarin and remdesivir concomitantly, and adjust the warfarin dose accordingly.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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