

Remdesivir-COVID-19: drug interactions in dentistry

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Abstract. – OBJECTIVE: Remdesivir is a nucleotide analogue prodrug that inhibits viral RNA polymerases. It has been recognized recently as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV5). We aimed at determining which drugs used in dentistry interact with Remdesivir in order to avoid adverse reactions that may worsen the condition of patients with COVID-19.

MATERIALS AND METHODS: A literature review was conducted to identify potential drug interactions between remdesivir (used in the treatment of COVID-19) and drugs prescribed in dentistry. The search was made in the databases PubMed and MEDLINE and official websites using key terms remdesivir, drug interactions and dentistry for articles published up to 31st July 2020.

RESULTS: According to the articles reviewed, a total of 279 drugs interact with Remdesivir. Two major interactions have been reported, 277 moderate drug interactions, and one with alcohol/food. The drug interactions involving drugs prescribed in dentistry are all moderate drug interactions and are (according to drug group): (1) antibiotics: azithromycin, clavulanate, doxycycline, erythromycin, levofloxacin; (2) antifungals: clotrimazole, fluconazole, itraconazole, ketoconazole; (3) non-steroidal anti-inflammatories (NAIDS): celecoxib, diclofenac, etodolac, flurbiprofen, ibuprofen, ketoprofen, ketorolac, mefenamic acid, naproxen, piroxicam.

CONCLUSIONS: It is clinically necessary for oral health professionals to be aware of possible drug interactions that may occur between remdesivir and drugs commonly prescribed in dentistry in order to prevent adverse reactions that may even endanger the life of a patient with COVID-19.

Key Words:

Remdesivir, COVID-19, Drug interactions, Dentistry, Antibiotics, Antifungals, Non-steroidal anti-inflammatories (NAIDS), Acetaminophen.

Introduction

Since the first cases were reported, infection by Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) has become a worldwide pandemic. COVID-19, the illness caused by SARS-CoV-2, is overwhelming health care systems all over the world^{1,2}. Recently, Remdesivir has been recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV5). Remdesivir is a nucleotide analogue prodrug that inhibits viral RNA polymerases and has exhibited *in vitro* activity against SARS-CoV-2³. Remdesivir was originally developed to treat Ebola virus. During the COVID-19 health crisis, the drug has been tested in clinical trials. The data obtained in one double-blind, randomized clinical trial, with a placebo as control (Study ACTT-1 del NIAID/ CO-US-540-5776) in hospitalized patients showed that patients with severe illness who received Remdesivir recovered in a shorter time than patients who received the placebo⁴. However, no differences were observed in the rate of recovery among patients receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at the start of treatment^{4,7}.

Such findings have led the European Commission to authorize its conditional marketing since 9th June 2020. This authorization is limited to its use for treating COVID-19 in adults and adolescents aged over 12 years with pneumonia who need oxygen. In Spain, until such time as Remdesivir is marketed effectively, the treatment can only be obtained *via* authorized clinical trials or by exceptional access due to special situations; this has been the case since the start of the health crisis⁴.

Remdesivir's potential mechanism of action against Coronavirus remains unclear although several reasons have been proposed to explain the

effects of Remdesivir³: firstly, Remdesivir can interfere with nsp12 polymerase even when exoribonuclease proofreading activity is intact⁸; secondly, Remdesivir can efficiently generate pharmacologically active nucleoside triphosphate (NTP) that acts as an alternative substrate and RNA-chain terminator⁸. The United States Food and Drug Administration has authorized the emergency use of Remdesivir for treating only hospitalized cases of COVID-19^{5,6}. Remdesivir is administered through infusion into a vein, usually once a day for up to 10 days (up to 5 days in Spain)⁴.

During recent months, the impact of COVID-19 on oral health has become clearer. Dziejczak et al⁹ report that due to indirect complex effects, intensified COVID-19 therapies, and multi-drug treatment, it is believed that some oral conditions could be aggravated by COVID-19. In this context, it is crucial for oral healthcare professionals to be aware of the drug interactions of any drug coming into use to treat COVID-19. A pharmacological interaction is defined as the modification of the pharmacodynamics and/or pharmacokinetics of the drug as a result of its administration together with other medicaments, dietary factors (nourishment, diet, medicinal plants), social habits (smoking, alcohol consumption), or underlying pathologies¹⁰.

The aim of this article was to determine which drugs used in dentistry (for treatment of pain and/or infections of the oral cavity) can interact with remdesivir in order to avoid adverse reactions that could worsen the situation of COVID-19 patients.

Materials and Methods

A literature review was conducted in the databases PubMed and MEDLINE identifying and selecting potential pharmacological interactions between remdesivir (used in the treatment of COVID-19) and the drugs prescribed in dentistry reported up to 31st July 2020. The key search terms applied were: *remdesivir*, *drug interactions* and *dentistry*. As the COVID-19 pandemic is an emerging, rapidly evolving situation, searches were also made in the official websites of: the National Institutes of Health (<https://www.nih.gov/health-information/coronavirus>); Centers for Disease Control and Prevention (CDC) (<https://www.cdc.gov/coronavirus/2019-ncov/index-sp.html>); U.S. Food and Drug Administration (FDA) (<https://www.fda.gov>); European Medicines Agency (EMA) (<https://www.ema.europa.eu/en>); and <https://www.drugs.com>.

Results

According to the articles reviewed, it is currently known that 279 drugs interact with Remdesivir. Two major interactions have been described, 277 moderate drug interactions, and one alcohol/food interaction^{11,12}. The major interactions are with chloroquine and hydroxychloroquine¹³; it has been observed that coadministration with chloroquine or hydroxychloroquine may reduce the therapeutic effects of remdesivir, and so its concomitant use must be avoided^{13,14}. Remdesivir's pharmacological interactions with drugs commonly prescribed in dentistry are all moderate drug interactions, and (according to drug group) are: (1) antibiotics: azithromycin, clavulanate, doxycycline, erythromycin, levofloxacin; (2) antifungals: clotrimazole, fluconazole, itraconazole, ketoconazole; (3) non-steroidal anti-inflammatories (NAIDS): celecoxib diclofenac, etodolac, flurbiprofen, ibuprofen, ketoprofen, ketorolac, mefenamic acid, naproxen, piroxicam^{11,12}.

Interaction With Alcohol (Ethanol)

Alcohol presents a moderate drug interaction with Remdesivir. As Remdesivir can cause liver problems, its use alongside other medications that can also affect the liver such as ethanol may increase that risk¹².

Interaction With Acetaminophen

Remdesivir can cause liver problems and so its use with other medications that can also affect the liver such as acetaminophen may produce hepatotoxic effects^{11,12}.

Interactions With Antibiotics

- According to data obtained in research and preliminary studies, an interaction between Remdesivir and azithromycin (in the same way as with the analgesic acetaminophen) may be associated with hepatotoxic effects.
- Within the macrolide family, erythromycin, a potent enzyme inhibitor, interacts with remdesivir in even more potent ways due to its mechanism of action¹⁵.
- Doxycyclines is an antibiotic belonging to the tetracycline group that prevents the growth of Gram-positive and Gram-negative bacteria. It may be prescribed to treat periodontal diseases and can interact with Remdesivir.
- Levofloxacin (second generation fluoroquinolone antibiotic that acts against Gram-negative

micro-organisms) also interacts with remdesivir.

All these antibiotics used in dentistry are hepatotoxic and must be avoided (if possible) whenever patients are being treated with remdesivir. It has also been suggested that there is an interaction between Remdesivir and clavulanate^{11,12}.

Interactions With Non-Steroidal Anti-Inflammatories (NAIDS)

Remdesivir presents potential interactions with the following NAIDS indicated for treating post-surgical pain in dentistry: Celecoxib (NSAID selective inhibitor of cyclooxygenase-2 [COX-2]), diclofenac, etodolac, flurbiprofen, ibuprofen, ketoprofen, ketorolac, mefenamic acid, naproxen, and pyroxicam^{11,12}.

Interactions With Antifungals

The articles reviewed state that the following systemic antifungals used in dentistry interact with Remdesivir: clotrimazole, fluconazole, itraconazole, ketoconazole^{11,12,15}.

Interaction With Carbamazepine

Carbamazepine may be used to treat trigeminal neuralgia; its interaction with Remdesivir may produce hepatotoxic effects^{11,12}.

Discussion

The World Health Organization designated COVID-19 as a global pandemic on March 11, 2020¹⁶. The drug for COVID-19 is distant¹⁷. This narrative review was conducted in response to the worldwide severity of the COVID-19 pandemic caused by SARS-CoV-2 and the development of a new drug that may turn about to be the treatment of choice for COVID-19¹⁸. Following COVID-19 treatment guidelines panel, there are insufficient data for the Panel to recommend either for or against the use of Remdesivir in patients with mild or moderate COVID-19⁹. Oral healthcare professionals play a fundamental role in the prevention and spread of COVID-19^{9,20}. In this context, dentists need to be aware of the potential risk of pharmacological interactions between Remdesivir and the drugs prescribed in dentistry. These interactions are based on transient treatment-emergent grade 1 or grade 2 elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which

have been observed during multiple-dose phase 1 studies in healthy volunteers placed in treatment with remdesivir^{11,12}. It was found that some ALT and AST elevations were associated with elevated graded prothrombin time, although there were no graded changes in International Normalized Ratio (INR)^{11,12}. Laboratory results for these subjects indicated no systemic sign of drug reaction. Transient elevations in liver transaminase levels were also observed in some participants during clinical studies of remdesivir for the treatment of acute Ebola virus disease and during compassionate use for the treatment of COVID-19. The mechanism of these elevations remains unknown^{11,12}.

The relevance of a particular drug interaction to a specific individual is difficult to determine. Major drug interaction has highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit. Moderate drug interaction has moderately clinically significant. Usually avoid combinations; use it only under special circumstances^{11,12}.

It has been observed in *in vitro* research that coadministration with chloroquine or hydroxychloroquine may reduce the therapeutic effects of remdesivir, and so concomitant administration must be avoided as this is considered a major pharmacological interaction¹³.

Interaction Between Remdesivir and Alcohol

This pharmacological interaction is very relevant to dentistry. It has been suggested that antiseptic mouth rinses may help to reduce the severity of COVID-19 and reduce the risk of transmission²⁰. It is known that alcohol presents a moderate drug interaction with Remdesivir and so oral healthcare professionals must be aware of this when it comes to prescribing antiseptic mouthrinse to patients in treatment with Remdesivir for COVID-19 and avoid mouthwashes containing alcohol. The main clinical manifestations that may appear due to this interaction are symptomatic of liver problems including: fever, chills, joint pain or swelling, nausea, vomiting, abdominal pain, unusual bleeding or bruising, skin rash, itching, loss of appetite, fatigue, dark urine, pale stools, and/or yellowing of the skin or eyes^{11,12}.

Interaction Between Remdesivir and Acetaminophen

Acetaminophen has analgesic and antipyretic properties and is mainly indicated for treating

slight or moderate pain²¹. When it is prescribed to relieve pain of orofacial origin, its moderate interaction with remdesivir may make it necessary to request liver function tests although prescription should be avoided if possible.

Interaction Between Remdesivir and Antibiotics: Azithromycin, Clavulanate, Doxycycline, Erythromycin, Levofloxacin

Regarding antibiotic prescription, great care must be taken with the macrolides, so azithromycin should be avoided when dealing with oral cavity infections. Likewise, clarithromycin and erythromycin must be avoided as it is an established fact that erythromycin (in particular) is a potent inhibitor of the hepatic oxidative enzyme system (oxidases) of the P450 cytochrome system¹⁵, which will aggravate hepatotoxic damage if patients are in treatment with Remdesivir.

Prescribing these antibiotics for orofacial infection must be avoided, particularly levofloxacin (antibacterial fluoroquinolone that acts on the DNA gyrase-DNA complex and on topoisomerase IV), which is used to treat acute bacterial sinusitis and complicated skin and soft tissue infections.

When there is no alternative therapeutic option available, current recommendation, are for dental professionals to carefully adjust the dose of the antibiotic and monitor liver function closely.

Interaction With Antifungals: Clotrimazole, Fluconazole, Itraconazole, Ketoconazole

These antifungals are potent enzyme inhibitors¹⁵ and so can increase blood plasma levels of Remdesivir leading to potential hepatotoxic damage.

Interaction with NAIDS: NAIDS are prescribed in daily dental practice, indicated for treating pain and inflammation of orofacial origin²². Diclofenac, etodolac, flurbiprofen, ibuprofen, celecoxib, ketoprofen, ketorolac, mefenamic acid, naproxen, piroxicam, must all be avoided in patients in treatment with remdesivir, due to the major risk of liver damage^{11,12}. This means that dental health professionals will be obliged to seek alternatives or adjust the dose as far as possible when treating patients presenting intense pain and/or inflammation in the oral cavity.

Interaction with carbamazepine: carbamazepine administration is indicated for treating pain associated with trigeminal neuralgia, this should be avoided in patients receiving Remdesivir due to the major risk of liver damage^{11,12}.

It should be noted that to date, no pharmacological interactions between Remdesivir and local anesthetics or vasoconstrictors that contain epinephrine or norepinephrine have been reported. Therefore, it would appear safe to employ the local anesthetics normally used in dentistry in patients in treatment with Remdesivir.

Conclusions

It is clinically necessary for dental healthcare professionals to be aware of possible pharmacological interactions between remdesivir and the drugs prescribed in dentistry in order to prevent adverse reactions that may endanger the lives of patients infected with COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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