Potential Interactions of Remdesivir with Pulmonary Drugs: a Covid-19 Perspective

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Abstract

In this letter, we discuss the potential interactions of remdesivir, the newly approved Covid-19 drug with pulmonary medications. These interactions have been summarized keeping the busy clinician in mind. While remdesivir has proven to be a safe medication generally, we here have enlisted the potential interactions of remdesivir that a clinician needs to be mindful of while prescribing the medication.

Keywords Remdesivir · Drug interactions · Pulmonology

For coronavirus, there are various therapeutic regimens under trial. Remdesivir has shown promise in initial studies for treating COVID-19 [1]. The mechanism of action for remdesivir has been studied in vivo and in vitro [1]. It acts by delaying the chain termination of RNA synthesis through competing with ATP for incorporation [1]. It has been studied mainly for the Ebola virus and respiratory syncytial virus, but the broad mechanism of action can be helpful in the treatment for SARS-CoV2 [1]. With the use of precision medicine, we can prevent, mitigate, and provide personalized pharmacologic treatment to the patients [2, 3].

Remdesivir is a substrate of CYP 3A4, CYP 2D6, and CYP 2C8, and its metabolism is mediated by hydrolase activity [4, 5]. The potential co-administration of inhibitors can lead to a potential increase in its levels [4, 5]. As remdesivir is a substrate of CYP 3A4, caution must be taken as it is co-administered

with many drugs, including above, as CYP enzymes are involved in the metabolism of a wide range of medications. However, the initial data coming out shows no harmful effects of these drug-drug interactions, due to its rapid metabolism by hydrolase and esterase [4, 5]. We conducted thorough search of Embase, PubMed, Scopus, PsycINFO, SciELO, and Web of Science. Since the drug is new and the information available is scarce, this commentary aims to review the potential interactions of remdesivir (Table 1).

Pharmacodynamic Interactions

Remdesivir has a low risk of significant pharmacodynamic interactions [6].

Pharmacokinetic Interactions

Steroids like dexamethasone and betamethasone induce CYP3A4 and thus will result in the rapid clearance of remdesivir [4]. Clinicians need to be cautious regarding this interaction. Rifampicin, rifabutin, and rifapentine strongly induce CYP3A4 enzyme [7]. These medications are used in the treatment of tuberculosis and leprosy. Co-administration of these medications with remdesivir can lead to rapid clearance and a significant decrease in remdesivir levels [6, 7]. This combination should not be co-administered [6, 7]. Bosentan is a drug primarily used in the treatment of pulmonary arterial hypertension. As it is mainly metabolized by CYP 3A4 and

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Table 1 Drug interactions of remdesivir

Drug interacting with remdesivir	Mechanism of action	Effect of drug interaction
Metamizole	Metamizole induces CYP3A4 and CYP2B6, and remdesivir is a substrate for the same	Leads to decreased levels of remdesivir by rapid clearance. There is no effect on the metabolism of metamizole due to inhibition of CYP3A4 by remdesivir
Rifampicin	Rifampicin strongly induces CYP3A4 and P-gp	Leads to decreased levels of remdesivir by rapid clearance. There is no effect on the metabolism of rifampicin
Rifabutin	Rifabutin strongly induces CYP3A4	Leads to decreased levels of remdesivir by rapid clearance. There is no effect on the metabolism of rifabutin
Rifapentine	Rifapentine strongly induces CYP3A4	Leads to decreased levels of remdesivir by rapid clearance. There is no effect on metabolism of rifapentine
Carbamazepine	Carbamazepine strongly induces CYP3A4 and UGT2B7	Leads to decreased levels of remdesivir, no effect on carbamazepine as remdesivir does not affect UGT's
Phenytoin	Phenytoin strongly induces CYP3A4	Leads to decreased levels of remdesivir. There is no effect on phenytoin as CYP2C9 metabolizes it
Phenobarbitone	Phenobarbitone strongly induces CYP3A4	Leads to decreased levels of remdesivir. There is no effect on phenytoin as CYP2C19, and CYP2C29 metabolize it
Primidone	Primidone is metabolized to phenobarbital and thus induces CYP3A4	Leads to decreased levels of remdesivir. There is no effect on primidone by inhibition of CYP3A4 by remdesivir as it is not metabolized by it
St John's wort	St John's wort strongly induces CYP3A4	It can lead to decreased levels of remdesivir. No effect is observed on metabolism of ST John's wort
Dexamethasone	Dexamethasone strongly induces CYP3A4	It can lead to decreased levels of remdesivir by rapid clearance but no effect on metabolism of dexamethasone
Betamethasone	Betamethasone strongly induces CYP3A4	It can lead to decreased levels of remdesivir by rapid clearance but no effect on metabolism of betamethasone

CYP 2C9, 4, 5, it has the potential of interaction with remdesivir. Although remdesivir causes inhibition of CYP 3A4, it is not expected to affect bosentan's metabolism. However, as bosentan is an inducer of CYP 3A4, it can potentially cause decreased levels of remdesivir [4]. Remdesivir does not interact with ambrisentan, epoprostenol, iloprost, macitentan, riociguat, selexipag, sildenafil, tadalafil, and treprostinil [6]. Remdesivir has no known interactions with any bronchodilators and beta-blockers and antivirals including oseltamivir [6]. Metamizole is a nonsteroidal anti-inflammatory drug (NSAID) used for chronic pain management in many countries. Metamizole gets hydrolyzed to 4-methylaminoantipyrine which is a substrate for CYP 3A4, 2B6, 2C8, and 2C9. No effect is expected due to remdesivir as it inhibits CYP3A4. However, as metamizole induces CYP3A4 moderately and CYP2B6 strongly in vitro, it can lead to depleted levels of remdesivir [6].

In summary, since remdesivir is metabolized quickly, the risk of interactions is exceptionally low. As we deal with critically ill COVID-19 patients with underlying comorbidities, clinicians need to be careful about the co-administration of various drugs with remdesivir as listed above and keep an eye out for new data that comes out.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Not required.

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