REVIEW

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COVID-19 Drug Interactions

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ABSTRACT

Elderly patients are at high risk of corona virus disease 2019 (COVID-2019) infection and severe COVID-19 patients are treated in intensive care units (ICU). Drug-drug interaction risk increased to 100% with eight or more medication use. Comorbidities in both elderly and ICU patients leading to polypharmacy and a higher risk for drug-drug interactions. Also, the organ dysfunctions due to COVID-19 may alter the pharmacokinetics of the drugs which may influence the severity of drug interactions. The severity, mechanisms, onset of action and clinical significance of the drug-drug interactions may vary. Detailed information on COVID-19 drug interactions is reported by The Liverpool Drug Interaction Group, however this paper was aimed to provide a quick guidance on these interactions for the clinicians. During the management of COVID-19, possibility of drug-drug interactions should be considered by clinicians to avoid any negative outcomes in the treatment process.

Keywords: COVID-19, Drug Interactions, Lopinavir/Ritonavir, Hydroxychloroquine, Polypharmacy

Introduction

Polypharmacy can be defined as 'concurrent use of more than five medication by a patient'. It has been associated with negative outcomes in patient treatment due to increased risk of drug related problems such as drug interactions, adverse effects and medication non-adherence (1). The elderly patients are at high risk group in terms of corona virus disease 2019 (COVID-2019) infection and according to the severity of the disease they may admitted to intensive care units (2). Polypharmacy is common in elderly and intensive care unit patients due to comorbidities and unstable conditions. The number of drug use is associated with risk of drug-drug interactions. Drug-drug interaction risk increased to 100% with eight or more drug use (3). Therefore these patients are at high risk of drug- interactions.

Currently, no specific treatment for COVID-19 is established. Turkish Ministry of Health Advisory Board on on Coronavirus Research published a report for the diagnosis, treatment and control of COVID-19. The recommendations on treatment were provided according to the available drugs (hydroxychloroquine, azithromycin, oseltamivir, lopinavir/ritonavir and favipiravir) in Turkey at the moment (4). All of these drugs have many potential DDIs that differ in clinical significance and they are metabolized in the liver (5). Besides other organ dysfunctions, acute kidney injury and liver dysfunction were also reported in COVID-19 patients (6) which may influence the severity of drug-drug interactions and adverse drug effects due to the pharmacokinetics changes.

Drug Interactions During COVID-19 Treatment

Lopinavir/ritonavir combination has a complex mechanism in terms of drug interactions. Lopinavir is primarily metabolized by cytochrome p450 (CYP) 3A enzymes and ritonavir is a potent inhibitor for CYP3A and CYP2D6. Inhibition of drug transporters such as p-glycoprotein, breast cancer resistance protein and induction of CYP1A2, CYP2B6, CYP2C19, CYP2C9, glucuronyl transferase enzymes also should be considered while using lopinavir/ritonavir combination. Hydroxychloroquine is metabolized by CYP2C8, CYP2D6, CYP3A4 and inhibits CYP2D6. Azithromycin is the preferred macrolide in terms of drug interaction due to its low risk for CYP450 mediated drug interactions. At the moment due to limited data available, favipiravir has low risk of drug interaction potential as well as oseltamivir (7). IL-6-induced suppression of CYP3A4 activity might reversed by tocilizumab, which may lead to decreased exposure to CYP3A4 substrates (8).

Table 1. Drug interactions with Lopinavir/ritonavir (adopted from 7)

Drug concentrations increased by LPV/r		Drug concentrations decreased by LPV/r	Drugs that increase LPV/r concentration	Drugs that decrease LPV/r concentration
- Alfa blockers	- Itraconazole	- Dipyridamole	- Clarithromycin	- Carbamazepine
- Amiodaron	- Ivabradine	- Gliclazide	- Posaconazole	- Dexamethasone
- Benzodiazepines	- Loperamide	- Glimepiride	- Voriconazole	- Phenytoin
- Beta blockers	- Midazolam	- Glipizide		- Rifampicin
- Calcium channel blockers	- NOA	- Morphine		
- Carbamazepine	- Ondansetron	- Moxifloxacin		
- Citalopram	- Propafenone	- Phenytoin		
- Clarithromycin	- Quetiapine	- Propofol		
- Clindamycin	- Ranolazine	- Theophylline		
- Cyclosporine	- Repaglinide	- Warfarin		
- Diazepam	- Salmeterol			
- Digoxin	- Saxagliptin			
- Escitalopram	- Sirolimus			
- Fentanyl	- Statins			
- Glyburide	- Steroids			
- Granisetron	- Tacrolimus			
- Haloperidol	- Valproic acid			
- Hydroxyzine	- Valsartan			
- Indapamide	- Zolpidem			
- Isosorbide dinitrate	- Zopiclone			

LPV/r: Lopinavir/ritonavir NOA: New oral anticoagulants

In this article, some examples of these interactions are listed below for a quick guidance to the clinicians (7, 9-11). The significance of these interactions may vary, therefore it should be assessed case by case. Please check (http://www.covid 19-druginteractions.org) for more detailed information.

- **Lopinavir+ritonavir** may increaseor decrease the concentrations of some drugs with concomitant use. In addition, **lopinavir+ritonavir** concentrations might be also decreased or increased by some drugs with concomitant use (Table 1). Dose adjustment, alternating drug use or monitoring should be considered case by case according to the severity and clinical significance of the interaction.

- Due to risk of QT prolongation with **lopinavir+ritonavir, hydroxychloroquine and azithromycin,** when they used in combination with each other or concomitant use with other drugs that prolong QT interval (such as quinolones, macrolides, ondansetron, antiarrhythmic agents, antidepressants and antipsychotics), clinicians should be aware of the increased risk of this adverse drug reaction. Therefore, electrocardiography monitoring and/or discontinuation of one of the drugs should be considered.

- **Hydroxychloroquine** concentrations might be decreased with inducers such as carbamazepine and rifampicin with concomitant use. Antacids may decrease the bioavailability of hydroxychloroquine with concomitant use. Therefore, hydroxychloroquine should be used 1-2 hours before or 4 hours after antacids.

- **Hydroxychloroquine** may increase the concentrations of amiodaron, dabigatran, edoxaban and immunosuppressants (such as cyclosporine, sirolimus, tacrolimus) with concomitant use. Dose adjustment of these drugs need to be considered according to clinical response or drug levels.

- Concomitant use of **hydroxychloroquine** with metronidazole, isoniazid or ethambutol may increase the risk of peripheral neuropathy especially in elderly (≥60 years) or diabetic patients. Patient monitoring is needed.

- Even though **azithromycin** has a low risk of drug interaction potential, concentrations of some narrow therapeutic index dugs such as digoxin, theophylline and warfarin might be elevated with concomitant use. Therapeutic drug monitoring of these drugs is recommended.

- Antacids may decrease the bioavailability of oral **azithromycin** with concomitant use. Therefore, oral azithromycin should be used 1-2 hours before or 4 hours after antacids.

- Concomitant use of **azithromycin** with atorvastatin or simvastatin may increase the risk of rhabdomyolysis. Patient monitoring or alternating with rosuvastatin or pravastatin should be considered.

- **Favipiravir** has low risk of drug interaction potential with concomitant use of theophylline and paracetamol.

- **Favipiravir** may increase the concentrations of pioglitazone or repaglinide with concomitant use that leads to risk of hypoglycemia. Blood glucose monitoring should be considered with concurrent use.

- **Oseltamivir** has low risk of drug interaction potential.
- **Tocilizumab** may increase the immunosuppressive effects of Anti-Tumor Necrosis Factor (Anti-TNF) agents, Biologic Disease-Modifying Antirheumatic Drugs (DMARDs), cladribine, infliximab, natalizumab, tacrolimus. Therefore, the concomitant use of tocilizumab with any of these medications should be avoided.
- **Tocilizumab** may also decrease the serum concentration of CYP3A4 substrates, therefore, monitor therapy is needed with concomitant use.

In addition to the risk of drug-drug interactions during COVID-19 treatment, the risk of interactions with herbal drugs is also exist such as significantly decreased efficacy of lopinavir/ritonavir or hydroxychloroquine with concomitant use of *St John's wort* (7).

Due to long half-life (about one month) of hydroxychloroquine, the risks of drug-drug interaction and QT prolongation may resume even after discontinuation of the drug and after hospital-discharge, therefore follow-up ECG evaluations and close monitoring of these patients should be considered especially for those taking any interacting medications or any medication with QT prolongation risk (12).

Conclusion

Drug-drug interactions can cause negative outcomes in patient treatment and triggers adverse drug effects, however they are preventable. The severity, mechanisms, onset of action and clinical significance of the drug-drug interactions may vary. Therefore, management of drug interaction is important as well as detection. Clinicians should consider the possibility of a drug-drug interaction when prescribing any new medications during the treatment of COVID-19 patients as well.

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