Brief Communication

Evaluation of the Prescribed Drugs to Elderly in a Tertiary Healthcare Center for Possible Drug Interactions with Investigational Drugs for COVID-19 Treatment

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Abstract

Objective: Earlier identifying drug interactions may help in risk reduction in elderly patients. **Methods:** Drug prescription data of 212 elderly patients of tertiary health care center had been analyzed for possible drug interactions with investigational drugs for COVID-19 treatment. Drug interaction had been checked from Stockley's Drug Interaction 2019 and Martindale the Complete Drug Reference 2017 and standard reference books of Pharmacology. **Findings:** Different types of drugs prescribed in the elderly were 260 and out of which 68 (26.36%) were in the category of fixed-dose combinations. Around 150 (70.75%) elderly patients were having one or more associated comorbidities. Thirty-five drugs prescribed to elderly had been found to cause drug interaction with investigational drugs for COVID-19. Possible drug interactions are mediated through CYP3A4 (eighteen patients), CYP2D6 (seven patients) isoenzymes, or P glycoproteins transporters (three patients). **Conclusion:** Possible drug interactions predicted in this study suggested need for modification of dose of drug or watchfulness for adverse effects. If these drug interactions are considered beforehand, complications can be prevented on account of these drug interactions in elderly who are suffering from COVID-19.

Keywords: *Drug interactions of drugs for COVID-19 in elderly, prevention of drug interaction of COVID-19 drugs*

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Introduction

During a COVID-19 pandemic, 80% of the United States deaths are in people over 65 years, and more affected were those who are around 80 with some underlying conditions.[1] Multiple drug use is common in the treatment of COVID-19, especially for patients with common diseases such as hypertension, diabetes, and other cardiovascular diseases, and their complications such as acute respiratory distress syndrome, shock, arrhythmia, and acute kidney injury.[2,3]

Elderly with comorbidity are at a significantly increased risk of severe disease following infection from COVID-19. Over 95% of these deaths occurred in those older than 60 years and more than 80% of deaths are occurring in individuals with at least one underlying comorbidity, in particular those with cardiovascular diseases or hypertension and diabetes.[4]

Common investigational drugs that are included in treatment guidelines of the National Institute of Health, National guidelines issued by the Government of India, AIIMS, Delhi, and various states are chloroquine/hydroxychloroquine, azithromycin, lopinavir and ritonavir drug combination, remdesivir and favipiravir, and tocilizumab are given in severe cases.[5-8]

Ritonavir is a strong inhibitor of CYP3A4 and it also inhibits CYP2D6.[9,10] Chloroquine and hydroxychloroquine are inhibitors of CYP2D6.[9]

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Ritonavir and azithromycin are inhibitors of P-glycoprotein transporter.[9] Ritonavir/lopinavir, chloroquine/hydroxychloroquine, and azithromycin are known for prolongation of QTc interval.[9,11]

Hence, this study was planned in the elderly to evaluate the possible drug interaction of the prescribed drugs with investigational drugs recommended for COVID-19 treatment. This study will help for cautious and appropriate use of drugs for the treatment of COVID-19 in elderly with or without comorbidities and prevent possible complications in these patients.

In this study, our primary objective was to find the possible drug interactions of the prescribed drugs with investigational drugs for COVID-19 treatment in elderly. Furthermore, we considered our secondary objectives as follows, to find out the proportion of different comorbid conditions observed in the tertiary health care center and to find out the proportion of drugs leading to the development of clinically significant drug interaction.

Methods

This study was a record review which included patients >65 years of either sex and taking two or more drugs. This study was carried out for the period of 2 months in a tertiary health care center after approval of the Institute Ethics Committee. For carrying out this study, data of 212 elderly patients had been taken from the already ongoing geriatric study (CTRI/2020/01/022852) in our tertiary health care center.[12] Medication data of 212 elderly patients had been entered in the Excel sheet and anonymized (identity had been be masked). This anonymized data was further analyzed for possible drug interactions of drugs prescribed in elderly with investigational drugs for COVID-19 treatment. Common drugs that are included in treatment guidelines as per the National guidelines and various states of India are chloroquine/hydroxychloroquine, azithromycin, lopinavir and ritonavir drug combination, favipiravir, remdesivir, and tocilizumab in severe cases. Drug interaction had been checked from Stockley's Drug Interaction, 12th edition, 2019, Goodman & Gillman's The Pharmacological Basis of Therapeutics, 13th edition, 2018, and Martindale the Complete Drug Reference 2017.[9,10,13]

Record of 212 elderly patients was analyzed in this study. Data were expressed as percentages and were evaluated qualitatively for possible drug interactions.

Results

Mean age of elderly patients in this study was 70.69 ± 5.59 years and 124 (58.49%) males and 88 (41.51%) females were recruited in this study. About 128 (60.38%) patients were on >5 drugs. Total drugs prescribed to 212 elderly patients were 1115 in this study, in that 332 (29.78%) were fixed-dose combinations (FDCs). Different types of drugs prescribed elderly were 260 and out which 68 (26.15%) were in the category of FDCs. The average number of drugs per prescription was 5.26.

Around 150 (70.75%) elderly patients were associated with one or more comorbidities. The patients were having hypertension/coronary artery disease, diabetes mellitus, asthma/chronic obstructive pulmonary disease, thyroid disease, arthritis and joint diseases, psychosis, and other disorders of the central nervous system (CNS), benign hypertrophy of prostate. Hypertension and diabetes with one or more associated comorbidities were seen in 96 (45.28%). In this study, 35 (13.46%) drugs prescribed to elderly had been found to cause drug interaction with investigational drugs for COVID-19 [Table 1]. Drug interaction with investigational drugs is mediated through CYP3A4 (eighteen patients), CYP2D6 (seven patients) isoenzymes, or P-glycoproteins transporters (three patients).

Drug interactions of investigational drugs for COVID-19 with the drugs prescribed to the elderly require a change in dose/drug/watchfulness for ADRs. Lopinavir/ritonavir increases the activity of escitalopram, clonazepam, alprazolam, chlordiazepoxide, carbamazepine, tetrabenazine, donepezil, tramadol, amlodipine, felodipine, diltiazem, metoprolol, propranolol, carvedilol, nebivolol, atorvastatin, rosuvastatin, tamsulosin, silodosin, linagliptin, and rifaximin. Chloroquine and hydroxychloroquine increase levels of amlodipine, betablockers, and tamsulosin whereas azithromycin will increase the level of atorvastatin and rosuvastatin.

Phenytoin decrease and spironolactone, paroxetine, and duloxetine increases the level of ritonavir-boosted lopinavir. No significant drug interactions had been observed for favipiravir and remdesivir with the prescribed drugs to elderly patients in this study.

QT prolongation occurs with various when used simultaneously with lopinavir/ritonavir, chloroquine/hydroxychloroquine, and azithromycin [Table 2].

Discussion

Mortality was observed >50% in the elderly who are suffering from COVID-19 and having one or more comorbidities such as diabetes mellitus, hypertension, or chronic diseases.[2,3,6] In this study, one or more associated comorbidities such as diabetes mellitus, hypertension, ischemic heart disease, hypothyroidism, CNS diseases, and respiratory diseases, joint diseases had been observed

Table1: List of drugs that cause significant drug interactions with investigational drugs for treatment of COVID 19

Name of the drugs prescribed to elderly	Number of patients (%)
Quetiapine	2 (0.94)
Olanzapine	2 (0.94)
Escitalopram	6 (2.83)
Paroxetine	1 (0.47)
Duloxetine	4 (1.89)
Amitriptyline	5 (2.36)
Nortriptyline	11 (5.19)
Clonazepam	10 (4.72)
Alprazolam	1 (0.47)
Chlordiazepoxide	1 (0.47)
Carbamazepine	1 (0.47)
Tetrabenazine	2 (0.94)
Donepezil	5 (2.36)
Tramadol	16 (7.55)
Amlodipine	65 (30.66)
Felodipine	1 (0.47)
Cilnidipine	10 (4.72)
Diltiazem	1 (0.47)
Metoprolol	24 (11.32)
Propranolol	2 (0.94)
Carvedilol	1 (0.47)
Nebivolol	1 (0.47)
Ranolazine	1 (0.47)
Atorvastatin	98 (45.28)
Rosuvastatin	12 (5.66)
Clopidogrel	20 (9.43)
Tamsulosin	26 (12.26)
Silodosin	2 (0.94)
Solifenacin	7 (3.30)
Linagliptin	2 (0.94)
Rifaximin	1 (0.47)
Moxifloxacin	1 (0.47)
Methotrexate	1 (0.47)
Ondansetron	1 (0.47)
Theophylline	1 (0.47)

in 96 (45.28%). The average number of drugs per prescription in this study was 5.26. Hence, elderly persons are at risk of developing various types of drug interactions.

Lopinavir and ritonavir both are CYP3A4 inhibitors and ritonavir is a strong inhibitor of CYP3A4.[10] This combination may increase levels of the prescribed drugs to elderly. In this study drugs such as quetiapine, escitalopram, clonazepam, chlordiazepoxide, alprazolam, donepezil, tramadol, amlodipine, felodipine, cilnidipine, diltiazem, ranolazine, atorvastatin, rosuvastatin, tamsulosin, silodosin, solifenacin, and linagliptin were prescribed to the elderly which are substrate for CYP3A4.[9,10,14,15] There are chances of increase in adverse effects or toxicities of these drugs. Hence, there is a need for dose modification or non interacting drugs can be preferred.

When quetiapine is given with lopinavir/ritonavir combination, there is an increased risk of priapism.[9] The UK manufacturer contraindicated the use of quetiapine with CYP3A4 inhibitors.[9] Both the drugs in combination increases the QTc interval. CYP3A4 inhibition may lead to the early development of arrhythmias due to QTc prolongation.[9] Ritonavir increases levels of clonazepam, alprazolam, chlordiazepoxide and there is a need to modify therapy/monitor closely as there are chances of potential toxicity. Hence, it is suggested to use alternative drugs if available or consider for lowering dose.[9,10] Ritonavir increases the effect of tramadol, hence there is a need to watch for sedation or decrease the dose of tramadol or adjust dosing interval.[9] Ritonavir increases levels of escitalopram and increases the risk of serotonin syndrome, in addition, it may increase QT interval leading to torsade des pointes (polymorphic ventricular tachycardia) can cause sudden cardiac death.[9,11] Lopinavir/ritonavir increases the level of carbamazepine, hence watch for drowsiness, vertigo, and vomiting.[9] Ritonavir will increase the effect of donepezil and hence some patients need to be watched for bradycardia or needed dose adjustment.[9]

Ritonavir increases the levels or effects of amlodipine, felodipine, cilnidipine, and diltiazem, and hence watch for dizziness, hypotension, and weakness.

Ritonavir will increase the effect of ranolazine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Ritonavir and azithromycin increase the level of ranolazine by inhibiting P-glycoprotein (MDR1) efflux transporter. Lopinavir/ritonavir and azithromycin are known to cause prolongation of QT interval. The dose of ranolazine need to be limited to 500 mg twice daily to avoid significant prolongation of QTc interval and possible risk of arrhythmia.[9]

Lopinavir/ritonavir and azithromycin increase the levels of atorvastatin and rosuvastatin by inhibition of CYP3A4/OATP1B1 transporter and there is an increased risk of myopathy. More risk of rhabdomyolysis had been observed in a short duration also when atorvastatin and rosuvastatin had been used with azithromycin. If coadministration cannot be avoided, limit atorvastatin dose to 20 mg/day and rosuvastatin dose to 10 mg/day.[9]

Lopinavir and ritonavir increase levels of tamsulosin by affecting hepatic/intestinal enzyme CYP3A4 and CYP2D6 (ritonavir) metabolism. Chloroquine

Table 2: Drugs prescribed in elderly than can lead to prolongation of QT interval with concomitant use with investigational drugs for COVID 19 treatment

Name of the drugs	Precautions/comments for use of these drugs
Lopinavir/Ritonavir increase (↑) QT interval with the following drugs	QT prolongation may lead to torsade des pointes*This can cause sudden cardiac death
Antipsychotic and antidepressant drugs	Patients may be asymptomatic or may present with presyncope, syncope or cardiac arrest, palpitations or may present with breathlessness owing to decreased cardiac output
Quetiapine	Avoid concomitant administration if QT interval more than 500 ms
Escitalopram	Avoid use with drugs that prolong QT and in patients with risk factors for prolonged QT interval
Amitriptyline/nortriptyline	ECG monitoring recommended
Antiemetic agents	Avoid with congenital long QT syndrome
Ondansetron	Ranolazine had dose dependent effect (>500 mg twice daily)
Chloroquine/hydroxychloroquineincrease (↑) QT interval with the following drugs	Avoid if electrolyte imbalance like hypokalaemia, hypomagnesemia and hypocalcaemia
Antipsychotic and antidepressant drugs	Treatment:
Olanzapine	Acquired QT prolongation - IV Magnesium sulphate/ Isoprenaline
Quetiapine	Congenital QT prolongation - Beta blocker like Propranolol/Nadolol
Escitalopram	
Amitriptyline/Nortriptyline	
Drugs for neurodegenerative disorders	
Tetrabenazine	
Drugs for angina	
Ranolazine	
Antimicrobial agents	
Moxifloxacin	
Antiemetic agents	
Ondansetron	
Drugs for benign prostatic hypertrophy/overactive bladder	
Solifenacin	
Azithromycin increase (↑) QT interval with the following drugs	
Antipsychotic and antidepressant drugs	
Olanzapine	
Quetiapine	
Amitriptyline/nortriptyline	
Escitalopram	
Antiemetic agents	
Ondansetron	
Antimicrobial agents	
Moxifloxacin	
Drugs for angina	
Ranolazine	

*Polymorphic ventricular tachycardia

also increases the level of tamsulosin by inhibiting CYP2D6. If needed to use simultaneously these drugs, then watchfulness needed for adverse effects such as dizziness, headache, and postural hypotension.[9,10] Tamsulosin is known to increase in QT interval, hence watch for arrhythmia when used with lopinavir/ritonavir and chloroquine**.** Furthermore, increased levels of silodosin were observed with this combination which can lead to ADRs such as dizziness, nasal congestion, and retrograde ejaculation.[15]

Ritonavir will increase the level or effect of solifenacin and there is a need for monitoring for antimuscarinic adverse effects such as xerostomia, constipation, blurring of vision, and dyspepsia.[9,10]

Ritonavir increases levels of linagliptin, and hence there is a need to watch for hypoglycemia and monitor blood glucose level.[9,10]

Lopinavir/ritonavir increases levels of rifaximin by P-glycoprotein (MDR1) efflux transporter. Hence we should be watchful for dizziness, fatigue, nausea, and peripheral edema produced by rifaximin and adjust the dosage accordingly. More problems if the patient is having a liver impairment.[9,10]

Ritonavir is also an inhibitor of CYP2D6 and will increase the level or effect of amitriptyline and nortriptyline, monitor for amitriptyline and nortriptyline toxicity. Tricyclics are known to cause prolongation of QT interval, hence alertness required for arrhythmia with these drugs.[9-11,13]

Ritonavir as well as hydroxychloroquine increases the effects of tetrabenazine by inhibiting hepatic enzyme CYP2D6 metabolism. Therefore, we should be watchful for hypotension, depression, suicidal tendency and also should consider for decreasing tetrabenazine dose by 50% if needed. Tetrabenazine is known to increase QTc interval, hence there are more chances of QT prolongation and arrhythmia with hydroxychloroquine and ritonavir-boosted combination.[9]

Ritonavir and chloroquine increase the levels/effects of metoprolol/propranolol/carvedilol/nebivolol by inhibiting CYP2D6, hence watch for signs/symptoms such as hypotension, bradycardia and shortness of breath.[9]

Various factors that can contribute to the prolongation of the QT interval are: (1) advanced age (2) female sex (3) congenital long QT syndrome (4) cardiac disease (5) thyroid disease, and (6) metabolic disturbances such as hypocalcemia, hypokalemia, and hypomagnesemia.[9] In the present, we had observed age (mean age 70.66 ± 5.59 years). 14 (6.6%) patients were having hypothyroidism and 155 (73.11%) patients were suffering from a cardiac disease such as hypertension or congestive heart failure or coronary vascular disease, hence the elderly population at risk of QT prolongation leading to torsade des pointes (polymorphic ventricular tachycardia). Patients may be asymptomatic or may present palpitations or breathlessness (decreased cardiac output) and some may present with presyncope, syncope, or cardiac arrest.[10] Drugs prolonging QT interval ondansetron, olanzapine, tetrabenazine, escitalopram, ranolazine, solifenacin, quetiapine, moxifloxacin, amitriptyline, nortriptyline, and moxifloxacin were prescribed to the elderly in this study. Concurrent use of these drugs may increase QT interval and with the contribution of risk factors may lead to the development of torsade des pointes causing dangerous arrhythmias.[9,11] Usually, if the QTc interval >500 ms, then the risk of torsade des pointes is more. Increase in QTc interval by 30–60 ms over baseline QTc 450 ms for males and 470 ms for females raise the concern for the arrhythmias.[9] Furthermore, the extent of QT prolongation depends on drug dose, escitalopram ritonavir, and ranolazine cause Prolongation of QTc with increasing dose, hence using the dose of these drugs on the lower side can also be helpful for preventing arrythmias.[9] Drugs having intrinsic ability to prolong QT interval and also inhibit metabolism of drug prolonging QT interval, lead to earlier development of dangerous arrhythmias.[9] This can very well correlated with prescribed drugs to the elderly in this study such as amitriptyline, tetrabenazine, and ranolazine whole metabolism of which is inhibited by drugs such as as lopinavir/ritonavir, hydroxychloroquine/chloroquine, or azithromycin and hence can increase QTc interval and cause arrhythmias.[11] In certain life threatening situations, simultaneous use of drugs is unavoidable, in such situations close ECG monitoring and careful evaluation of other risk factors are necessary.[9]

Drugs like phenytoin can decrease in the level of ritonavir-boosted lopinavir hence patients may not get the therapeutic benefit of ritonavir for COVID 19 when used simultaneously.[12,14] In other way, spironolactone, paroxetine, duloxetine increases levels of lopinavir/ritonavir combination may be of therapeutic advantages sometimes.[9,16]

Favipiravir is metabolized in the liver by aldehyde oxidase (AO) in cytosol. Selective estrogen receptor modulators, H_2 receptor antagonist, calcium channel blockers, antiarrhythmics such as propafenone, and tricyclic antidepressants such as amitriptyline are potent AO inhibitors.[17] There are no evidences for drug interactions with felodipine, amlodipine, and amitriptyline which were prescribed to elderly in this study. Hence, no/less risk of drug interaction of favipiravir with the prescribed drug in this study. Favipiravir inhibits sulfate transferase; hence the recommended maximum daily doses of acetaminophen are 3 grams with favipiravir.[17]

There is no clear-cut evidence whether CYP isoenzyme and P glycoprotein (gp) transporter affect the overall metabolism of remdesivir and its metabolites. However, it was advised that remdesivir should not be co-administered with strong CYP or P-gp inducers. It can be given with strong CYP inhibitors to get therapeutic benefits.[18]

Drugs used for COVID 19 and in elderly for treatment of various comorbidities are substrate/inhibitor/inducer for CYP3A4/CYP2D6 hence may cause significant drug interaction which may further require modification of the dose of drug. There need for watchfulness of adverse effects. QT prolongation property of drugs like ritonavir, hydroxychloroquine, chloroquine, azithromycin can lead torsade des pointes which further can cause Sudden cardiac death. If these drug interactions are considered beforehand, complications can be prevented on account of these drug interactions in elderly who are suffering from COVID-19.

Authors' Contribution

Yogendra Keche, Nitin Gaikwad, and Suryaprakash Dhaneria participated in study design and concept. Yogendra Keche and Apoorva Joshi participated in data collection and prepared the manuscript. Suryaprakash

Dhaneria and Nitin Gaikwad commented and critically reviewed the manuscript and all authors approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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