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Short Communication

The Potential Determinants and Adverse Outcomes of Clinically Significant Drug-Drug Interactions in COVID-19 Ward

Ali Arab[1], Kimia Masafi[1], Shahram Habibzadeh[2], Saeid Sadeghieh-Ahari[3] and Sara Mostafalou[1]*

1. Department of Pharmacology & Toxicology, School of Pharmacy, Ardabil University of Medical Sciences, Ardabil, Iran
2. Department of Infectious Diseases, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran
3. Department of Social Medicine, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran

Abstract

Background: Identification of the risk factors of potential Drug-Drug Interactions (DDI) and investigation of their adverse outcomes.

Methods: The cross-sectional study was a retrospective analysis of a patient cohort treated at the COVID-19 ward of the Imam Khomeini hospital in Ardabil, northwest of Iran. The study included a randomized selection of patients who were admitted to the ward over three months in 2020. The demographic, medical data and drug-drug interactions of 150 randomly selected patients during three months in the COVID-19 ward of the Imam Khomeini hospital in Ardabil, northwest of Iran was analyzed.

Results: At least one potential DDI was identified in 96% of patients. The number of drugs was the only risk factor for the occurrence of DDI. In addition to the number of drugs and prescribers, all types of interactions (except type X) were associated with an increased risk of mortality and duration of hospitalization.

Conclusion: DDI are highly prevalent in the COVID-19 ward. A reduction in potential adverse effects and unwanted outcomes of pharmacotherapy is possible by reducing the number of prescribed drugs and preventing drug-drug interactions.

Keywords: Adverse effects, COVID-19, Drug interactions

*** Corresponding author**
Sara Mostafalou, PhD
Department of Pharmacology & Toxicology School of Pharmacy, Ardabil University of Medical Sciences, Ardabil, Iran
Tel: +98 45 3352 2437
Fax: +98 45 3352 2197
Email: s.mostafalou@gmail.com

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Introduction

COVID-19 is an infectious disease that has become a significant health issue in the current decade. Recognition of this disease as one of the leading causes of death worldwide at a specific period prompted many scientists to collaborate in finding effective therapeutics (1). During the COVID-19 pandemic, many efforts were made to decrease the duration of hospitalization and deaths from this disease. The favorable results of early clinical trials on the efficacy of repurposed medications, such as Azithromycin, Hydroxychloroquine, Famotidine, Naproxen, Doxycycline, Remdesivir, Favipiravir, Lopinavir, Ritonavir, Interferons, and Bevacizumab, led to the prescription of various drugs to infected patients (2). Even assuming the fact that each of these drugs alone may promote the outcomes of COVID-19 patient, addition of these medications to patient's therapeutic regimen without considering other medications used by the patient, brings many risks.

The relationship between the increase of the number of medications used by patients and the increases of unintentional Adverse Drug Reactions (ADRs) has been studies in multiple studies. Drug-Drug Interactions (DDIs) are one of the most common causes of ADRs and are responsible for changing the efficacy and safety of drugs. Moreover, several factors have been identified as the risk factors of DDIs, including increasing patients age, the number of medications used by patient (also polypharmacy), comorbidities, and length of hospitalization (3,4). Although DDIs are predictable and often preventable, they are still considered an important source of mortality and morbidity.

Although the same studies on DDIs have been conducted in different regions of Iran but not Ardabil, the present study offers several advantages including a more detailed analysis of DDIs, a broader range of resources to check interactions, and a larger study population (5). Therefore, the aim of this study was to identify the risk factors of potential DDIs in the COVID-19 ward and their effect on mortality and length of hospitalization.

Materials and Methods

The cross-sectional study was a retrospective analysis of a patient cohort treated at the COVID-19 ward of the Imam Khomeini hospital in Ardabil, northwest of Iran. The study included a randomized selection of patients who were admitted to the ward over three months in 2020. The only inclusion criterium was admission to the COVID-19 ward without any limitation in sex, age, and underlying diseases. The exclusion criteria were the absence of an initial definitive diagnosis of COVID-19 and the administration of fewer than two drugs. Cochran's formula was used to calculate the study population. DDI were assessed using UpToDate (types X, D, C, B, and A), Micromedex software (Major and Moderate) and the drug interaction facts book (Pharmacokinetic, Pharmacodynamic, Rapid and Delayed).

Multiple logistic regression was used to assess the potential risk factors of each type of DDI, using patient characteristics (age and sex), number of prescribers, number of prescribed medications, and length of hospitalization as independent variables and the number of DDIs of each type as dependent variables.

Furthermore, the association of the patient's demographic and medical data and the number of interactions with the occurrence of death and length of stay (less than 7 days *vs*. 7 days or more) was also investigated by binary logistic regression. The p-values lower than 0.05 were considered statistically significant. All data analysis was carried out using SPSS 26.0. All procedures described above was approved by the ethic committee of Ardabil university of medical science.

Results

Almost half of the total 150 selected patients (50.7%) were male. The mean age of patients was 60.2 years old ranging from 1 to 93 years old. Sex and age of patients was not associated with the risk of discharge by death and length of hospitalization, significantly. However, the patients had up to 15 prescribers, only 28.6% had more than 6 and the majority (42.8%) had 4 to 6 prescribers. Patients stayed at the ward between 1 to 20 days with an average of 6.6. Sixteen percent of patients were discharged due to death. 14.6 medication were on average prescribed for each patient. Pharmacodynamic, C, and Moderate Type were the most frequent DDIs, respectively. A further description of the population is mentioned in table 1.

Table 1. Risk factors of discharge caused by the death and length of stay

	Discharge by death				Length of stay (discharged alive) less than 7 days *vs.* 7 days or more			
Variables	**n(mean)**	**OR**	**CI 95%**	**p-value**	**n(mean)**	**OR**	**CI 95%**	**p-value**
Sex	150	1.182	0.492-2.837	0.708	126	1.574	0.775-3.198	0.210
Age	150(60.2)	1.021	0.996-1.047	0.102	126(59.0)	1.009	0.991-1.028	0.314
Number of drugs	2184(14.6)	1.201	1.095-1.318	p<0.001	1719(13.6)	1.200	1.103-1.305	p<0.001
Number of prescribers	(5.3)	1.340	1.148-1.563	p<0.001	(4.9)	1.291	1.095-1.521	0.002
Number of DDIs								
All types	1781(11.9)	1.085	1.038-1.134	p<0.001	1325(10.5)	1.085	1.033-1.140	0.001
X	57(0.4)	1.135	0.696-1.852	0.612	46(0.4)	1.525	0.967-2.405	0.069
D	237(1.6)	1.267	1.038-1.545	0.020	178(1.4)	1.281	1.040-1.577	0.020
C	1085(7.2)	1.125	1.059-1.195	p<0.001	777(6.2)	1.087	1.017-1.161	0.014
Rapid	98(0.6)	1.349	1.019-1.786	0.036	66(0.5)	1.648	1.045-2.597	0.031
Delay	189(1.3)	1.420	1.153-1.749	0.001	129(1.0)	1.493	1.127-1.978	0.005
PK	313(2.1)	1.225	1.049-1.432	0.010	231(1.8)	1.210	1.026-1.427	0.024
PD	1544(10.3)	1.088	1.037-1.142	0.001	1149(9.1)	1.091	1.032-1.152	0.002
Major	277(1.8)	1.474	1.146-1.896	0.003	214(1.7)	1.306	1.005-1.695	0.046
Moderate	1263(8.4)	1.102	1.044-1.165	0.001	932(7.4)	1.088	1.024-1.156	0.006

CI: Confidence Interval, OR: Odd Ratio, PD: Pharmacodynamic interaction, PK: Pharmacokinetic interaction, DDI: Drug-Drug Interactions.

Among all types of DDIs, X type was the only type that its occurrence was not associated with increase odds of discharge by death and more than seven days of hospitalization, significantly. Patients with major and delayed type DDIs had the highest odds of discharge by death, and patients with X and rapid type DDIs had the highest odds of hospitalization longer that seven days, respectively.

Among independent variables including, age, sex, number of prescribes, number of drugs, and length of hospitalization, the results of linear regression have only shown a significant positive relationship between the number of prescribed drugs and all individual types of DDIs.

In addition to the number of drugs and prescribers, all types of clinically important DDIs (except type X) were related to an increase in the risk of death and duration of hospitalization, significantly (Table 1).

Discussion

DDIs occurs when two or more drugs interact with each other in a way that alters their expected effect. However, in some cases this combination is beneficial and intended. What concern us the most is that in most cases these alteration lead to unwanted side effects, reduced efficacy, and or potential harmful reactions (6). This study indicated the concerning results of the presence of at least one DDI in 96% of patients' medical records. A review of the most frequent DDIs in this study indicates that none of these interactions were beneficial. Investigation of the risk factors and awareness of the adverse outcomes might be helpful to prevent further undesirable outcomes by prompting corrective actions more seriously.

Herein, since increased mortality rate and duration of hospitalization are the most obvious results of attenuation of desirable therapeutic effects of prescribed drugs, the effect of DDIs on these two outcomes was discussed. Actually, many factors influence these two outcomes. For instance, there is a logical relationship between the disease severity and the number of medications prescribed to a

Table 2. Most frequently identified pairs of type D and X DDIs

	Frequency	Risk rating	Onset of ADRs	Severity	Mechanism and potential ADRs
Heparin/Naproxen	17	D	ND	Moderate	PK-may enhance the anticoagulant effect of Heparin
Fentanyl/Midazolam	11	D	ND	Major	PK-may enhance the CNS depressant effect of Fentanyl
Enoxaparin/Aspirin	11	D	ND	Moderate	PD-may enhance the anticoagulant effect of Enoxaparin
Aspirin/Naproxen	10	D	ND	Moderate	PD and PK-may enhance the adverse effects of NSAIDs
Heparin/Clopidogrel	10	D	ND	Moderate	PD-may enhance the anticoagulant effect of Heparin
Kaletra/Atorvastatin	8	D	ND	Moderate	PD-may increase the serum concentration of Atorvastatin
Losartan/Captopril	6	D	ND	Moderate	PD and PK-may enhance the adverse effects of ACEIs
Pethidine/ Diphenhydramine	6	D	ND	Major	PD-may enhance the CNS depressant effect of pethidine
Kaletra/Salmeterol	6	X	delayed	Major	PK-may increase the serum concentration of salmeterol

ADRs: Adverse Drug Reactions Kaletra: the brand name of Lopinavir and Ritonavir ND: Not Determined PD: Pharmacodynamic interaction PK: Pharmacokinetic interaction.

patient. Definitely, for more precise conclusion, it is recommended to adjust the result of the study by the severity of patients' disease, but evaluation of patient severity is beyond the scope of such a retrospective study. Though, the purpose of this study is to point out what prescribers may overlook. Simply increasing the number of prescribed medications does not necessarily improve patient's condition. In fact, it can abolish the intended beneficial effects of other essential medications and threaten his/her life.

Consistent with previous similar studies, the number of prescribed drugs was considered the main risk factor for the occurrence of DDIs. There are multiple approaches to decrease the number of potential DDIs. To have the pharmacological mechanism and classifications of prescribed drugs in mind helps the prescriber avoid therapeutic duplications (*e.g.*, the combination of antithrombotic drugs), and reduce the number of drugs and the total number of DDIs, subsequently. Previously, studies have shown a direct association between the number of prescribers and risk of receiving inappropriate medication (7). The present study, reported a more than expected number of prescribers for each patient. Involvement of clinical pharmacist to actively participate in ward rounds and review the medication plans is another established solution, but unfortunately the hospital lacked this capability at the time of the study. Conducting periodical studies to investigate DDIs and outcomes of prescribed medications and informing the prescribers of its results can also be an informative but weak and delayed alternative.

It appears that drugs such as Heparin, Naproxen, Enoxaparin, Aspirin, Atorvastatin, and Kaletra® (Lopinavir/Ritonavir) that their efficacy on COVID-19 patients have been studied before, had the most frequent and clinically important DDIs (2). For better clarification, the risk rating, severity, mechanism, and potential adverse effects of the most frequently identified potential DDIs are shown in the table 2. Holding meetings and committees for rational medication prescription and reviewing the medication before adding it to the therapeutic regimen of a specific disease may also be thoughtful (8). For instance, reviewing the frequent and potential DDIs of Kaletra® by prescribers could decrease multiple major and moderate interactions.

As expected, the results of this study revealed a stronger association between outcomes and types D and major DDIs compared to types C and moderate DDIs, which indicates that the severity of DDIs is related to the strength of results.

As well, a stronger association was observed between pharmacokinetic DDIs and outcomes compared to pharmacodynamics. It might be concluded that comparatively more severe pharmacokinetic DDIs were neglected by prescribers. According to the fact that pharmacokinetic DDIs take place at levels of absorption, distribution, metabolism, and excretion of drugs, prevention of them is only possible when the prescriber has sufficient knowledge of the pharmacokinetics of prescribed drugs or has been previously informed of the potential adverse drug reaction.

Interestingly, delayed interaction had a stronger association with discharge by death and a weaker association with length of stay compared to rapid DDIs, respectively. It might be inferred that manifestations of rapid DDIs which occur within 24 hours of administration of drugs were well-managed in the COVID-19 ward, since it is easier to correlate the symptoms to recent administer medications but when it comes to delayed DDIs in which the adverse reactions takes time to appear and their effects may resemble disease progression, an increase in mortality has resulted from the decrease in patient safety.

Conclusion

The finding of the present study reveals a high prevalence of clinically important DDIs in the COVID-19 ward. The reported direct impact of DDIs on the mortality rate and length of hospitalization of COVID-19 patients reminds us the fact that efforts to reduce DDIs can play an important role in reducing unwanted complications and treatment costs. Considering the number of prescribed drugs as the main risk factor for the occurrence of DDIs, decreasing the number of drugs is the most efficient way to reduce number of DDIs. To achieve more accurate and reliable statistical results, it is recommended to conduct studies with a larger population and consideration of additional factors including severity of disease and underlying diseases. So far, this study serves as a warning about the need for further investigation into patients prescribed medications in hospitals.

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Ethical approval

Ethical approval was granted by the Ardabil University of Medical Sciences Research Ethics Committee (Reference no: IR.ARUMS.REC.1399.290).

Conflict of Interest

There was no conflict of interest in this manuscript.

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