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ORIGINAL PAPER

Drug-Drug Interactions in Patients with COVID-19: A Retrospective Study at a Tertiary Care Hospital in Eastern India

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ABSTRACT

Introduction: *Coronavirus disease 2019 (COVID-19) is an emerging viral infection without any approved treatment. Investigational therapies for COVID-19 may cause clinically important drug-drug interactions (DDIs). We aimed to study drug-drug interactions (DDIs) and their risk factors in hospitalised COVID-19 patients.*

Methods: *We conducted a retrospective study in a tertiary care hospital dedicated to COVID-19 patients. The Lexi-Interact database was used to investigate clinically important DDIs. The database output, including interacting drug pairs, risk rating, reliability rating, mechanism, and management, was evaluated.*

Results: *Medical records of 200 COVID-19 patients were analysed. All patients had at least one clinically important DDI. More than half of interactions were associated with hydroxychloroquine and azithromycin, the most commonly prescribed medications for the management of COVID-19. Concomitant drugs for comorbid conditions leading to polypharmacy were significantly associated with the occurrence of this.*

Conclusion: *There is a higher chance of DDI, which necessitates ongoing care evaluation and therapy adjustment. Drugs used to treat COVID-19 should be carefully selected.*

Keywords: drug-drug interactions (DDIs), COVID-19 patients, polypharmacy, adverse drug reactions (ADRs).

INTRODUCTION

The novel coronavirus pneumonia (COVID-19) is caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) infection (1). SARS-CoV-2 emerged in Wuhan, China, in December 2019, and has rapidly spread across the world due to its high transmissibility and pathogenicity (2). On the 30th of January 2020, the World Health Organization (WHO) declared it a public health emergency of international concern and a global pandemic was declared on the 11th of March 2020.

Drug-drug interaction (DDI) is defined as a modification of the effects of one drug (the object drug) by the prior or concomitant adminis-

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tration of another drug (the precipitant drug) (3). DDIs are one of the causes of adverse drug reactions (ADRs) and sometimes therapeutic failure following multiple drug therapies (4, 5).

The patient population most affected by severe forms of COVID-19 includes not only the elderly (> 65 years), but also younger people living with co-morbidities such as obesity, hypertension and type 2 diabetes (6–8). Most of these particularly fragile patients benefit from chronic treatment, often combining several drugs. The worsening of COVID-19 sometimes requires treatment in intensive care units (ICUs), combining sedation and mechanical ventilation. In the most serious forms, multi-organ failure can be observed (*e.g.* cardiac, renal, and hepatic, along with thrombotic issues) (9-11), which requires poly-pharmacy (benzodiazepines, opioids, anticoagulants, calcium channel blockers, glucocorticoids, etc.).

Several therapeutic strategies (hydroxychloroquine, azithromycin, remdesivir, corticosteroids, etc.) have been tried for COVID-19 treatment (12-15). These drugs are given in combination, or along, with drug used for associated co-morbidities in several COVID-19 patients. Some of the drugs being tested are likely to interact with chronic treatment as well as the treatment used in patient resuscitation. Such DDIs largely result from their pharmacokinetic properties (*e.g.*, induction or inhibition of cytochrome P450 (CYP) isoenzymes, competition in renal elimination) as well as their pharmacodynamics properties (*e.g.*, QT prolongation). In addition to these interactions, there is a large inflammatory component in COVID-19 patients, which can modify the pharmacokinetic behaviour of the drugs used (*e.g.*, down-regulation of CYP isoenzymes, organ failure, modification of plasma protein concentrations) (16, 17).

These interactions can lead to the development of various side effects and therapeutic failure in COVID-19 patients. There is a lack of prescribing pattern on the basic of theoretical knowledge of drug interaction in the management of COVID-19 infection. Therefore, we designed this study to assess the clinically relevant DDIs of COVID-19 candidate drugs and concomitant drugs used for comorbidities. This study will provide an insight into a safe and rational use of medicines among COVID-19 patients. ❑

MATERIALS AND METHODS

This retrospective observational study was carried out in All India Institute of Medical Science (AIIMS), Patna, (Bihar) India on COVID-19 patients admitted to AIIMS Patna from March 2020 to August 2020, after obtaining approval from Institutional Ethics Committee, AIIMS Patna.

Two hundred (n=200) medical records of COVID-19 patients confirmed by RTPCR were evaluated from the Medical Record Department (MRD) of AIIMS Patna. Data were recorded on a standardised format on Microsoft Excel summarising information about age, sex, presenting complaints and comorbidities. Data regarding the number of drugs prescribed for COVID-19 and comorbid conditions, hospital stay, and ICU admission were gathered. Patients with daily prescriptions of two or more drugs were considered for analysis, while those who were receiving more than two drugs, intravenous fluids, multivitamins (Vit. C, Vit. D), minerals (Zn), and blood products were excluded.

DDI in each prescription was assessed using Lexicomp drug interaction software (18) and then categorised for severity, risk rating, mechanism, and reliability rating for drug interactions.

Severity rating indicates the reported or possible magnitude of an interaction outcome and it is classified as **minor** (causes minimal effects that are usually tolerable – do not require medical intervention), **moderate** (potential for significant interaction, but do not meet the criteria for major severity – generally requires monitoring of therapy and in few cases, medical intervention may be needed), **major** (potential for serious interaction – typically requires medical intervention and/or close monitoring) and **contraindicated** (drugs which should never be used together because of severe life-threatening interactions) (19).

Risk rating reflects both the level of urgency and the nature of actions necessary to respond to an interaction (18). Based on risk rating, the interactions are classified into five categories, including A (no known interaction), B (no action needed), C (monitor therapy), D (modify regimen), and X (avoid combination) (20). The DDIs were also categorized as pharmacokinetic and pharmacodynamics interactions based on their underlying **mechanisms**.

Reliability rating indicates the quantity and nature of documentation for an interaction and is scaled as excellent (E), good (G), or fair (F) (18).

Statistical analysis

Data were capture on Microsoft Excel. The drug interactions detected by the software were documented. Data were analysed as mean, frequency, percentage and interquartile range using SPSS software version 16.0. ❑

RESULTS

Two hundred medical records of patients with confirmed COVID-19 were evaluated. Table 1 shows the patients' demographic and clinical characteristics. Of the total study population, 73.5% were male. A median number of six medications (IQR, 6–7) were administered to patients. Diabetes (9%) was the most common comorbidity, followed by hypertension (8%), hypothyroidism (2.5%) and hypercholesterolemia (2%). The most commonly prescribed drugs for COVID-19 patients include hydroxychloroquine (93.5%), followed by azithromycin (90.5%), paracetamol (89.5%) and enoxaparin (70.5%) (Figure 1).

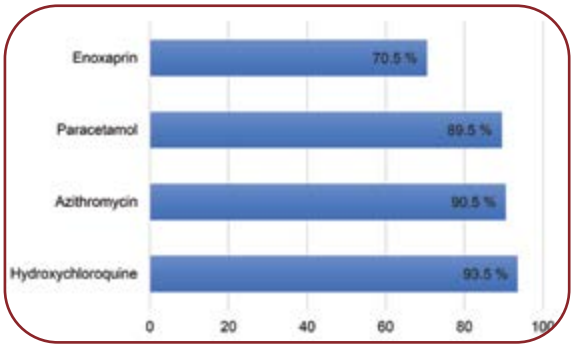

FIGURE 1. Commonly prescribed drugs for COVID-19

Study population	N (%)
No. of patients	200
Age (years)	
<40	79 (39.50%)
40-60	81 (40.50%)
>60	40 (20%)
Hospital stay, median (IQR), days	13 (12-16)
No. of drugs, median (IQR)	6 (6-7)
Sex	
Male	147 (73.5%)
Female	53 (26.5%)
ICU admission	11 (5.5%)
Any comorbidities	
Diabetes	18 (9%)
Hypertension	16 (8%)
Diabetes + hypertension	6 (3%)
Hypothyroidism	5 (2.5%)
Hypercholesterolemia	4 (2%)
Gout	1 (0.5%)
Obesity	3 (1.5%)
Psychosis	2 (1%)
Chronic kidney disease	1 (0.5%)
Left para-aortic paraganglioma	1 (0.5%)
Pulmonary embolism	1 (0.5%)

TABLE 1. Patients' demographic and clinical characteristics

Concomitant medication	Severity	Mechanism	Effect	Recommendation
Azithromycin	Moderate	PK	QT prolonging effect	Closely monitor ECG
Glimepiride	Moderate	PK	Increases risk of hypoglycaemia	Monitor therapy
Metformin	Moderate	PK	Increases risk of hypoglycaemia	Monitor therapy
Olanzapine	Minor	PK	QT prolonging effect	Closely monitor ECG
Ondansteron	Minor	PK	QT prolonging effect	Closely monitor ECG
Norfloxacin	Moderate	PK	Enhances the hypoglycaemic effect	Monitor therapy
Flecainide	Minor	PK	QT prolonging effect	Closely monitor ECG
Metoprolol	Moderate	PK	Increases serum level of metoprolol	Monitor therapy
Pioglitazone	Moderate	PK	Increases risk of hypoglycaemia	Monitor therapy
Gliclazide	Moderate	PK	Increases risk of hypoglycaemia	Monitor therapy
Teneligliptin	Moderate	PK	Increases risk of hypoglycaemia	Monitor therapy
Insulin glargine	Moderate	PK	Increases risk of hypoglycaemia	Monitor therapy
Saroglitazar	Moderate	PK	Increases risk of hypoglycaemia	Monitor therapy
Voglibose	Moderate	PK	Increases risk of hypoglycaemia	Monitor therapy

TABLE 2. DDIs between hydroxychloroquine and concomitant medication their severity, mechanism, effect and recommendation based on Lexicomp drug interaction software

Concomitant medication	Severity	Mechanism	Effect	Recommendation
Ondansteron	Moderate	PK	QT prolonging effect	Closely monitor ECG
Salbutamol	Minor	PK	QT prolonging effect	Closely monitor ECG
Norfloxacin	Minor	PK	QT prolonging effect	No action needed
Flecainide	Moderate	PK	QT prolonging effect	Closely monitor ECG
Tacrolimus	Moderate	PK	Serum level of tacrolimus	Monitor therapy
Atorvastatin	Moderate	PK	Azithromycin enhances the myopathic effect of statin	Monitor therapy
Teneligliptin	Minor	PK	QT prolonging effect	No action needed
Levofloxacin	Moderate	PK	QT prolonging effect, Ventricular arrthymias	Monitor therapy

TABLE 3. DDIs between azithromycin and concomitant medication their severity, mechanism, effect and recommendation based on Lexicomp drug interaction software

Drug combination	Severity	Mechanism	Effect	Recommendation
Prazosin + Atenolol	Moderate	PD	Enhances the hypotensive effect	Monitor therapy
Salbutamol + Atenolol	Moderate	PD	Reduces the bronchodilatory effect	Monitor therapy
Telmisartan + Heparin	Moderate	PK	Enhances the effect of hyperkalaemia	Monitor therapy
Enoxaparin + Sulfasalazine	Moderate	PK	Increases the risk of bleeding	Monitor therapy
Aspirin + Ascorbic acid	Minor	PK	Decreases the level of ascorbic acid	No action needed
Pioglitazone + Glimipride Metformin	Major	PK	Enhances the hypoglycemic effect	Consider therapy modification
Glicazide + Atenolol	Moderate	PK	Enhances the hypoglycemic effect	Monitor therapy
Paracetamol + Ondansetron	Minor	PK	Decreases the analgesic effect	No action needed
Levofloxacin + Ondansetron	Moderate	PK	QT prolonging effect	Monitor therapy
Paracetamol + Phenytoin	Moderate	PK	Decreases serum level of paracetamol	Monitor therapy
Dexamthasone Hydrochlorothiazide	Moderate	PK	Enhances hypokalaemic effect of diuretics	Monitor therapy
Dexamthasone + Voglibose	Moderate	PK	Diminishes antidiabetic effect	Monitor therapy
Hydrochlorothiazide Voglibose	Moderate	PK	Diminishes antidiabetic effect	Monitor therapy
Enoxaparin + Losartan	Moderate	PK	Enhances the hyperkalaemic effect	Monitor therapy

TABLE 4. DDIs between concomitant medication their severity, mechanism, effect and recommendation based on Lexicomp drug interaction software

Tables 2 and 3 show the interactions between hydroxychloroquine and azithromycin with concomitant medications. Pharmacokinetic interaction is common with moderate severity. QT prolongation and increased risk of hypoglycaemia requires close monitoring of ECG and therapy.

Pharmacokinetic interaction is common with moderate severity for comorbid medications. The DDI between Pioglitazone+Glimipride+Metformin is of major severity, leading to hypoglycaemic effect, and therapy modification may be required. Other interactions require therapy monitoring (Table 4).

The highest number of DDIs were found in prescriptions of 6–7 drugs (n=102; 58.28%); however, the average number of DDIs *per* prescription was highest in those with 8-10 drugs (1.8) (Table 5).

In our study we noted 35 types of DDIs, of which 27 (77.14%) were "moderate" in severity, seven (20%) minor and one (3%) major, totalizing 175 interactions (Figure 2). There were 94% pharmacokinetic interactions and 6% pharmacodynamics interactions (Figure 3).

Reliability rating indicates the quantity and nature of documentation for an interaction. Reli-

No. of prescribed drugs	No. of prescriptions (total 200)	No. of DDIs (total 175)	Average number of DIs *per* prescription
2-5	58	55 (31.42%)	0.95
6-7	132	102 (58.28%)	0.77
8-10	10	18 (10.28%)	1.8

TABLE 5. Number of drug-drug interactions and number of drugs *per* prescription

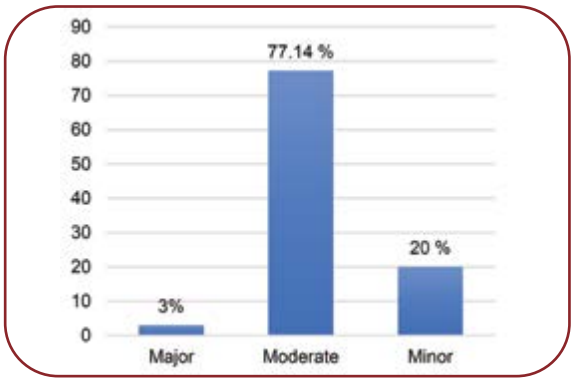

FIGURE 2. Types of DDIs based on severity

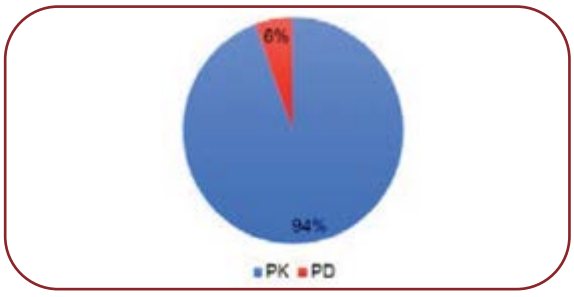

FIGURE 3. Types of DDIs based on mechanism

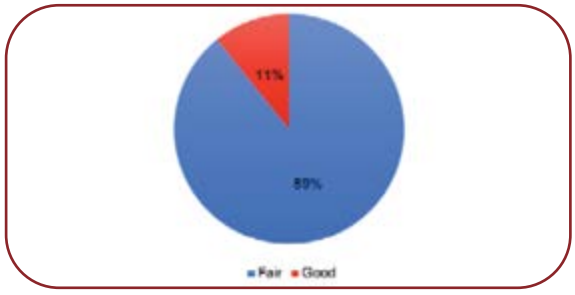

FIGURE 4. Reliability rating of DDIs

Potential outcome	No. (%)
Hypoglycemia	12 (32.43%)
QT prolonging effect	11 (29.72%)
Therapeutic failure of beta blockers	4 (10.81%)
Therapeutic failure of paracetamol	2 (5.40%)
Hyperkalemia	2 (5.40%)
Hyperglycemia	2 (5.40%)
Therapeutic failure of heparin	1 (2.70%)
Hypokalemia	1 (2.70%)

TABLE 6. Common potential outcome of DDIs

ability rating in our study was fair [33 (89.19%)] and good [4 (10.81%)] (Figure 4).

The most common potential outcomes included hypoglycaemia (n=12, 32.43%), QT prolonging effect (n=11, 29.72%), and therapeutic failure of beta blockers (n=4, 10.81%). Hyperglycemia, therapeutic failure of heparin, hyperkalemia as well as hypokalemia were other potential outcome noted by us (Table 6). ❑

DISCUSSION

The concept of DDI, which has been studied in pharmacology, poses a challenge to clinicians, being often difficult to identify and diagnose, especially in clinical conditions which are associated with comorbidities. Given that there is no specific treatment for COVID-19, attempts have been made to use polypharmacy for the management of infected patients, which was acknowledged to carry a significant risk of DDIs. Therefore, we conducted this retrospective study to identify the severity, risk rating, frequency, reliability rating, mechanism and recommendation of DDIs in hospitalized patients with COVID-19. We assessed 200 medical records using Lexicomp drug interaction software.

The severity assessment of DDIs (using Lexicomp drug interaction software) showed that most of them were of moderate severity (77.14%), followed by minor (20 %) and major (3%) interactions. This sequence is comparable to a study conducted by Amir Ali Mahboobipour and Shadi Baniasadi (23).

We noted a high prevalence (6-7 drugs) of polypharmacy in our study population. Many studies have considered polypharmacy to be the concurrent use of five or more drugs (21, 22), while extensive polypharmacy is deemed to be the use of 10 or more in adults (24). The high level of DDI prevalence in our study could be due to several factors such as comorbidities, presence of extensive polypharmacy, and long duration of hospital stay, and many others (25, 26). An important finding in this study was the rela-

tionship between the number of drugs prescribed to a patient and the incidence of DDIs. Although the interactions were more numerous in prescriptions of 6–7 drugs, the average DDIs *per* prescription were the highest in those that had 8-10 drugs (1.8 *per* prescription). Similar findings were reported by Sherin and Udaykumar (27), who found that the average number of PDDI *per* prescription increased with an increase in the number of concomitant medications. This suggests that an increase in polypharmacy is linked to an increase in the number of DDIs, which is an established fact in several other studies as well (28). Other studies also convey a clear and strong evidence that the risk of DDI is proportional to the number of medications (29-31). We found that 94% were pharmacodynamic interactions and 6% pharmacokinetic interactions, which is in contrast to another study in a paediatric population (65% pharmacodynamic *vs.* 35% pharmacokinetic interactions) (32).

Hypoglycaemia was found to be the most common potential outcome in our study (32.43%), which contributed mainly by an interaction between hydroxychloroquine and oral hypoglycaemic agents. As earlier mentioned, it is generally of moderate severity and requires monitoring therapy. In our study, we have also found potential instances of QTc prolongation (29.72%). In a study conducted by Baniasadi *et al*, prolongation of QTc interval was found to be the most common potential outcome (19).

The strength of our study lies in the fact that DDI research is minimal among COVID-19 patients. Hence, information provided by our research can both improve the understanding of prescription pattern and encourage physicians to carefully prescribe certain medications to these patients. Apart from this, our study can provide a framework for future pharmacotherapeutic studies.

This was a single-center study with a small sample size. Hence, our findings cannot be generalized. Interactions identified by using Lexicomp software were DDIs, and we did not assess whether they manifested in patients or not, which is a major limitation. Although Lexicomp drug interaction checker is a very reliable (supported by Wolters Kluwer Health) and commonly used system for identifying PDDIs, discrepancies have been found in the identification and grading of DDIs severity between different systems (33, 34). Hence, the results of this study may not correlate well with those of other similar studies that have used different DDI-checking systems. Furthermore, discrepancies have been reported between the number of PDDIs detected with electronic systems and those evaluated by doctors as clinically relevant (35), which could be a potential limitation to our study. ❑

CONCLUSION

There is no definitive treatment of COVID-19 to date. Therefore, there is a trend towards the use of polypharmacy in the management of COVID-19. Our findings reveal an increased risk of DDI, which needs continuous monitoring of treatment and therapy modification. Therefore, drugs should be chosen carefully in the management of COVID-19. This study will be helpful to provide an insight for safe and rational use of medicine among COVID-19 patients. Our study has few limitations, including small sample size and discrepancies in identification and grading of DDI severity between different system. Therefore, further research with a large sample size is required. ❑

Conflicts of interest: none declared.

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Ethical approval and informed consent: The study was approved by the Institutional Ethics Committee, AIIMS Patna (Ref. No. AIIMS/Pat/IEC/2020/559 Dated 08/09/2020). Waiver of informed consent was granted as patient details were anonymized and only medical records of hospitalized COVID-19 patients were analysed.

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