Indonesian Journal of Pharmacy

VOL 36 (2) 2025: 348–359 | RESEARCH ARTICLE

Potential Drug Interaction of Corticosteroids and Symptomatic Therapy in COVID-19 Patients at RSUD Banyumas, Indonesia

Heny Ekowati[1], Nialiana Endah Endriastuti[1], Zulfanida Akmelati[1] and Sarmoko[2]*

1. Department of Pharmacy, Faculty of Health Sciences, Universitas Jenderal Soedirman, Purwokerto 53123, Indonesia
2. Department of Pharmacy, Faculty of Science, Institut Teknologi Sumatera, South Lampung 35365, Indonesia

Article Info

Submitted: 07-01-2023
Revised: 31-05-2024
Accepted: 03-06-2024

*Corresponding author
Sarmoko

Email:
sarmoko@fa.itera.ac.id

ABSTRACT

The global spread of COVID-19 poses significant health risks, underscoring the need for effective treatments. The concurrent use of corticosteroids and symptomatic medications in COVID-19 patients may lead to drug interactions. This study investigates potential drug interactions between corticosteroids, symptomatic drugs, and other medications in COVID-19 patients at Banyumas Hospital, Indonesia. Employing a descriptive observational methodology with a retrospective design, the study included all COVID-19 inpatients at the Banyumas Hospital between June 2020 and June 2021. Potential drug interactions were analyzed using the Drugs Interaction Checker on Drugs.com and Lexicomp on UpToDate. The analysis included 334 patients, identifying potential drug interactions categorized into pharmacokinetics (189 cases, 38.10%), pharmacodynamics (264 cases, 53.23%), and unknown mechanisms (44 cases, 8.87%). Regarding severity, the interactions were classified as major (50 cases, 10.08%), moderate (204 cases, 41.13%), and minor (243 cases, 48.1%). Patients with COVID-19 are at risk for potential drug interactions, most of which cannot be avoided. It is important to select appropriate corticosteroid and symptomatic drugs uses and manage therapy appropriately to reduce the incidence of potential drug interactions. While the potential for drug interactions is prevalent in COVID-19 patients taking corticosteroids and symptomatic drugs, many of these drug interactions may not have clinical significance. Therefore, further empirical research is essential to thoroughly assess these potential interactions and devise strategies to mitigate any serious adverse effects they may cause.

Keywords: COVID-19, potential drug interactions, corticosteroids, symptomatic

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome-Corona Virus-2 (SARS-CoV-2), has emerged as a global pandemic (Lai et al., 2020). With a mortality rate of approximately 2% (Gavriatopoulou et al., 2021), Indonesia documented its first case on March 2nd, 2020, and experienced a significant escalation thereafter. By June 2022, Indonesia reported a cumulative total of 6,090,509 confirmed cases and 156,740 fatalities (WHO, 2022). Severe cases of COVID-19 can lead to Acute Respiratory Distress Syndrome (ARDS), a severe respiratory failure marked by acute hypoxemia (Gibson et al., 2020; Meng et al., 2020).

In managing COVID-19, corticosteroids such as dexamethasone, methylprednisolone, and prednisone are crucial for mitigating cytokine storm syndromes in severe cases, potentially preventing ARDS (Gavriatopoulou et al., 2021; Mattos-Silva et al., 2020). Additionally, symptomatic treatments targeting specific manifestations of COVID-19—ranging from N-acetylcysteine for its mucolytic and antioxidative properties, paracetamol for fever reduction, gastric acid suppressants such as ranitidine and omeprazole for digestive ailments, to ondansetron,

a serotonin receptor antagonist for nausea and vomiting—are integral in the clinical management of mild to moderate COVID-19 (Ray et al., 2020; Bayat et al., 2021; Kemenkes RI, 2021; Yong, 2021).

However, the intersection of COVID-19 therapy with existing treatments for chronic conditions, often involving polypharmacy, raises significant concerns about drug-drug interactions (Hodge et al., 2020). Notably, corticosteroids may attenuate the efficacy of remdesivir, paracetamol's co-administration with favipiravir could heighten hepatotoxicity risks, ranitidine may alter the renal excretion of concurrent medications (Ahmad et al., 2016), omeprazole's interaction with CYP2C19 stimulators may decrease its area under the curve (AUC), and ondansetron's combination with azithromycin could prolong the QT interval (Lemaitre et al., 2020; Rezaee et al., 2021). Recognizing and managing these potential interactions is imperative to ensure the safety and efficacy of COVID-19 treatment regimens. This study aims to investigate potential drug interactions between corticosteroids, symptomatic drugs, and other medications in COVID-19 patients at Banyumas Hospital, Indonesia.

MATERIALS AND METHODS

Ethical clearance

This study received ethical approval from the Health Research Ethics Committee of Banyumas Hospital (Certificate No. 116/KEPK-RSUDBMS/VI/2021).

Design

The study was a descriptive observational study with a retrospective design. The purpose of this study was to identify the potential interaction of corticosteroids as well as drugs for symptomatic therapy in COVID-19 patients at Banyumas Regional Hospital in the period June 2020-June 2021.

Population and sample

The population included all hospitalized COVID-19 patients in the June 2020-June 2021 at Banyumas Regional Hospital. Total sampling was employed, meaning that all units in the population met the inclusion and exclusion criteria were sampled. The inclusion criteria were patients having a verified diagnosis of COVID-19, patients receiving corticosteroids and/or drugs for symptomatic therapy, and patients with complete medical records. The exclusion criteria were pregnant women, as the pharmacokinetics of pregnant women differ from other patients.

Data source

Data were obtained from the medical records of COVID-19 patients hospitalized in June 2020-June 2021 in the medical record installation of Banyumas Regional Hospital. The data included patient identity (name, medical record number, age, gender, primary and secondary diagnosis), supporting examination results (PCR swab results), and information on drug use (drug name, dose, route, frequency, and time of administration).

Analysis

Descriptive analysis was performed using the Drug Interaction Checker on Drugs.com, Lexicomp via UpToDate, and relevant literature. Univariate analysis was used to identify the number of COVID-19 patients and their characteristics, including age, gender, comorbidities, corticosteroid use, and symptomatic therapies. Potential drug interactions were categorized by their mechanism (pharmacokinetics, pharmacodynamics, and unknown) and severity (major, moderate, minor) as well as their management. Data were presented in tables or figures.

RESULTS AND DISCUSSION

A total of 373 medical records obtained between June 2020 and June 2021, with an average of 30 to 40 records per month. After applying the inclusion and exclusion criteria, 334 patient records were included in the study, while 39 were excluded. The exclusions were due to the following reasons: 11 patients diagnosed with COVID-19 did not receive corticosteroids and drugs for symptomatic therapy, 18 patients had suspected but unverified COVID-19, and 10 patients were pregnant.

Patient characteristics

Between June 2020 and June 2021, Banyumas Regional Hospital admitted 334 patients diagnosed with COVID-19. The cohort consisted of 148 males (44.3%) and 186 females (55.7%). The largest age group was the early elderly (46–55 years), representing 23.65% of the patients. A substantial number of patients (n = 242) presented with comorbidities, the most common being hypertension (35.1%), followed by diabetes mellitus (23.0%) (Figure 1).

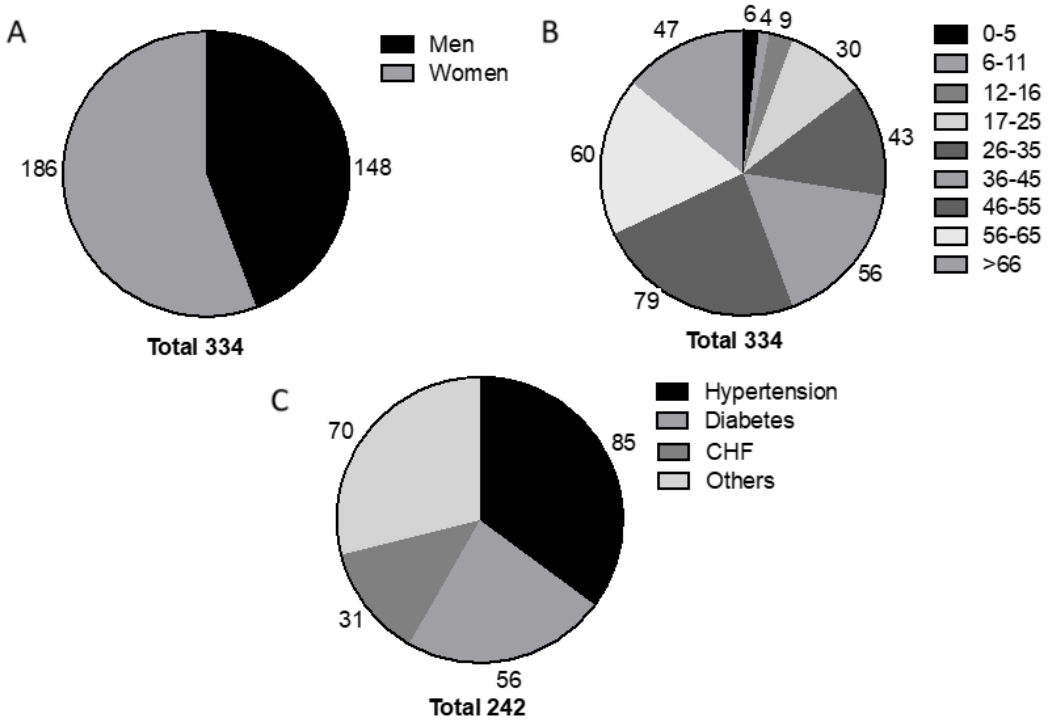

Figure 1. Patients' characteristic admitted to Banyumas Regional Hospital with COVID-19. (A) sex, (B) age, (C) comorbidities. DM: diabetes mellitus, CHF = congestive heart failure

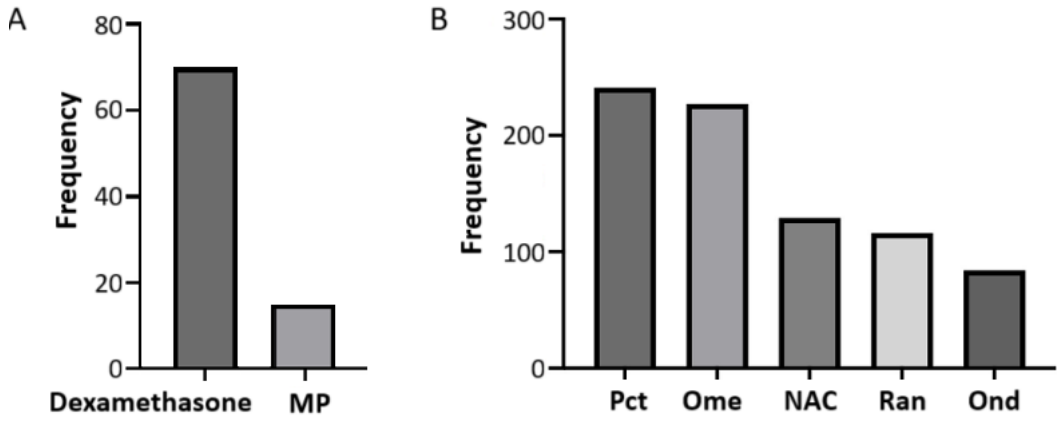

Figure 2. Drug use profile of COVID-19 patients hospitalized at Banyumas Regional Hospital. (a) Corticosteroid use, (b) Symptomatic drug use. MP: methylprednisolone, PCT: paracetamol, Ome: omeprazole, Ran: ranitidine, Ond: ondansetron

Drug use profile

This study describes the medication profile of COVID-19 patients who were hospitalized at Banyumas Hospital from June 2020 to June 2021 (Figure 2). The data indicated that dexamethasone was the most frequently used corticosteroid, administered to 70 patients. Methylprednisolone was used by 15 patients. Regarding symptomatic treatment, paracetamol was the most commonly prescribed medication, used by 241 patients. Additionally, other medications were used as follows: omeprazole (227 patients), N-acetylcysteine (129 patients), ranitidine (116 patients), and ondansetron (84 patients) (Figure 2).

Table I. Potential interaction of corticosteroid drugs and drugs for symptomatic therapy based on its pharmacokinetics in hospitalized COVID-19 patients at Banyumas Regional Hospital

No	Mechanisms	Drug combination	Frequency (n=496)	Percentage (%)
1	**Pharmacokinetics absorption**	Paracetamol >< Metoclopramide	41	8.27
2		Paracetamol >< Codeine	22	4.44
3		Omeprazole >< Acetylsalicylic acid	5	1.01
4		Dexamethasone >< Sodium Bicarbonate	2	0.40
5		Methylprednisolone >< Sodium bicarbonate	1	0.20
6		Omeprazole >< Digoxin	1	0.20
7		Omeprazole >< Nifedipine	1	0.20
8		Paracetamol >< Domperidone	1	0.20
9		Paracetamol >< Clidinium	1	0.20
10		Paracetamol >< Chloroquine	1	0.20
11		Ranitidine >< Sodium bicarbonate	1	0.20
12	**Pharmacokinetics metabolism**	Paracetamol >< Favipiravir	93	18.75
13		Omeprazole >< Alprazolam	4	0.81
14		Ranitidine >< Ketorolac	3	0.60
15		Dexamethasone >< Alprazolam	1	0.20
16		Dexamethasone >< Codeine	1	0.20
17		Methylprednisolone >< Alprazolam	1	0.20
18		Omeprazole >< Diazepam	1	0.20
19		Omeprazole >< Chlordiazepoxide	1	0.20
20		Omeprazole >< Midazolam	1	0.20
21		Omeprazole >< Tocilizumab	1	0.20
22		Paracetamol >< Fenofibrate	1	0.20
23		Paracetamol >< Isoniazid	1	0.20
24	**Pharmacokinetics excretion**	Ranitidine >< Metformin	3	0.60
Total pharmacokinetics mechanism			**189**	**38.10**

Potential drug interaction

An analysis of medical record data revealed that majority of the patients, 305 patients (91.32%) experienced potential drug interactions, whereas 29 patients (8.68%) did not. These potential drug interactions were categorized into three types: pharmacokinetics, pharmacodynamics, and unknown mechanisms. Pharmacokinetic interactions, which may affect drug absorption, distribution, metabolism, and excretion, were observed in 189 cases (38.10%) of patients experiencing potential pharmacokinetic drug interactions. Furthermore, potential pharmacodynamic drug interactions were identified in 264 cases (53.23%) (Table I-III).

Based on the Drug Interaction Checker on Drugs.com and Lexicomp on UpToDate, the severity of potential drug interactions was graded as minor, moderate, and major (Table IV). Among COVID-19 patients hospitalized at Banyumas Regional Hospital between June 2020 and June 2021, 52 cases (10.48%) were identified as having potential major drug interactions. Moderate-level interactions were noted in 202 cases (40.73%), while minor-level interactions were the most common, observed in 243 cases (48.99%). This distribution suggests that most potential drug interactions were of minor severity.

Our analysis indicates a higher admission rate of female patients than male patients. However, global data demonstrates a higher mortality rate among male COVID-19 patients than their female counterparts (Nawawi et al., 2021). This discrepancy may be partly explained by differences in receptor expression and distribution, which are pivotal in the viral infection pathway, thereby influencing both pathogenesis and the identification of therapeutic strategies.

Table II. Potential interaction of corticosteroid drugs and drugs for symptomatic therapy based on its pharmacodynamics in hospitalized COVID-19 patients at Banyumas Regional Hospital

No	Mechanism	Drug Combination	Frequency (n=496)	Percentage (%)
1		Paracetamol >< Remdesivir	72	14.52
2		Dexamethasone >< Levofloxacin	28	5.65
3		Ondansetron >< Azithromycin	24	4.84
4		Ondansetron >< Levofloxacin	24	4.84
5		Dexamethasone >< Furosemide	13	2.62
6		Ondansetron >< Hydroxychloroquine	13	2.62
7		Omeprazole >< Furosemide	11	2.22
8		Ondansetron >< Codeine	6	1.21
9		Omeprazole >< Pioglitazone	6	1.21
10	**Pharmacodynamics synergism**	Methylprednisolone >< Levofloxacin	5	1.01
11		Ondansetron >< Moxifloxacin	4	0.81
12		Ondansetron >< Chloroquine	3	0.60
13		Methylprednisolone >< Furosemide	2	0.40
14		Methylprednisolone >< Meloxicam	2	0.40
15		Ondansetron >< Domperidone	2	0.40
16		Dexamethasone >< Bisacodyl	1	0.20
17		Dexamethasone >< Ketorolac	1	0.20
18		Dexamethasone >< Moxifloxacin	1	0.20
19		Dexamethasone >< Ciprofloxacin	1	0.20
20		N-acetylcysteine >< Glyceryl trinitrate	1	0.20
21		Ondansetron >< Bisacodyl	1	0.20
22		Ondansetron >< Erythromycin	1	0.20
23		Ondansetron >< Chlorpromazine	1	0.20
24		Ondansetron >< Metronidazole	1	0.20
25		Ondansetron >< Salbutamol	1	0.20
26		Ondansetron >< Ciprofloxacin	1	0.20
27		Paracetamol >< Ondansetron	19	3.83
28		Dexamethasone >< Salbutamol	4	0.81
29		Dexamethasone >< Amlodipine	3	0.60
30		Dexamethasone >< Candesartan	3	0.60
31		Dexamethasone >< Spironolactone	3	0.60
32		Methylprednisolone >< Amlodipine	2	0.40
33		Dexamethasone >< Bisoprolol	1	0.20
34	**Pharmacodynamics antagonism**	Dexamethasone >< Ramipril	1	0.20
35		Methylprednisolone >< Insulin Glargine	1	0.20
36		Methylprednisolone >< Terbutaline	1	0.20
37		Dexamethasone >< Amlodipine	3	0.60
38		Dexamethasone >< Candesartan	3	0.60
39		Dexamethasone >< Spironolactone	3	0.60
40		Methylprednisolone >< Amlodipine	2	0.40
41		Dexamethasone >< Bisoprolol	1	0.20
42		Dexamethasone >< Ramipril	1	0.20
43		Methylprednisolone >< Insulin Glargine	1	0.20
44		Methylprednisolone >< Terbutaline	1	0.20
	Total pharmacodynamics mechanism		**264**	**53.23**

Table III. Potential interaction of corticosteroid drugs and drugs for symptomatic therapy based on its unknown mechanism in hospitalized COVID-19 patients at Banyumas Regional Hospital

No	Mechanism	Drug combination	Frequency (n=496)	Percentage (%)
1		Paracetamol >< Ranitidine	41	8.27
2		Omeprazole >< Glyceryl trinitrate	1	0.20
3	**Unknown**	Omeprazole >< Isosorbide dinitrat	1	0.20
4		Omeprazole >< Ciprofloxacin	1	0.20
	Total unknown mechanism		**44**	**8.87**

Table IV. Potential interactions of corticosteroid drugs and drugs for symptomatic therapy based on their severity in hospitalized COVID-19 patients at Banyumas Hospital

No	Severity	Drug combination	Frequency (n=496)	Percentage (%)
1		Dexamethasone >< Levofloxacin	28	5.65
2		Ondansetron >< Hydroxychloroquine	13	2.62
3	**Major**	Methylprednisolone >< Levofloxacin	5	1.01
4		Ondansetron >< Moxifloxacin	4	0.81
5		Dexamethasone >< Moxifloxacin	1	0.20
6		Dexamethasone >< Ciprofloxacin	1	0.20
		Total major severity	**52**	**10.48**
7		Paracetamol >< Remdesivir	72	14.52
8		Ondansetron >< Azithromycin	24	4.84
9		Ondansetron >< Levofloxacin	24	4.84
10		Dexamethasone >< Furosemide	13	2.62
11		Omeprazole >< Furosemide	11	2.22
12		Ondansetron >< Codeine	6	1.21
13		Omeprazole >< Pioglitazone	6	1.21
14		Omeprazole >< Alprazolam	4	0.81
15		Dexamethasone >< Amlodipine	3	0.60
16		Dexamethasone >< Candesartan	3	0.60
17		Dexamethasone >< Spironolactone	3	0.60
18		Ondansetron >< Chloroquine	3	0.60
19		Ranitidine >< Metformin	3	0.60
20		Methylprednisolone >< Amlodipine	2	0.40
21		Methylprednisolone >< Furosemide	2	0.40
22		Methylprednisolone >< Meloxicam	2	0.40
23	**Moderate**	Ondansetron >< Domperidone	2	0.40
24		Dexamethasone >< Bisacodyl	1	0.20
25		Dexamethasone >< Bisoprolol	1	0.20
26		Dexamethasone >< Codeine	1	0.20
27		Dexamethasone >< Ketorolac	1	0.20
28		Dexamethasone >< Ramipril	1	0.20
29		Methylprednisolone >< Insulin Glargine	1	0.20
30		N-acetylcysteine >< Glyceryl Trinitrate	1	0.20
31		Omeprazole >< Diazepam	1	0.20
32		Omeprazole >< Digoxin	1	0.20
33		Omeprazole >< Chlordiazepoxide	1	0.20

Continue of Table IV. Potential interactions of corticosteroid drugs and drugs for symptomatic therapy based on their severity in hospitalized COVID-19 patients at Banyumas Hospital

No	Severity	Drug combination	Frequency (n=496)	Percentage (%)
34		Omeprazole >< Midazolam	1	0.20
35		Ondansetron >< Bisacodyl	1	0.20
36		Ondansetron >< Erythromycin	1	0.20
37		Ondansetron >< Chlorpromazine	1	0.20
38		Ondansetron >< Metronidazole	1	0.20
39		Ondansetron >< Salbutamol	1	0.20
40		Ondansetron >< Ciprofloxacin	1	0.20
41		Paracetamol >< Fenofibrate	1	0.20
42		Paracetamol >< Isoniazid	1	0.20
		Total moderate severity	**202**	**40.73**
43		Paracetamol >< Favipiravir	93	18.75
44		Paracetamol >< Metoklopramide	41	8.27
45		Paracetamol >< Ranitidine	41	8.27
46		Paracetamol >< Codeine	22	4.44
47		Paracetamol >< Ondansetron	19	3.83
48		Omeprazole >< Acetylsalicylic acid	5	1.01
49		Dexamethasone >< Salbutamol	4	0.81
50		Ranitidine >< Ketorolac	3	0.60
51		Dexamethasone >< Sodium bicarbonate	2	0.40
52	**Minor**	Dexamethasone >< Alprazolam	1	0.20
53		Methylprednisolone >< Alprazolam	1	0.20
54		Methylprednisolone >< Sodium bicarbonate	1	0.20
55		Methylprednisolone >< Terbutaline	1	0.20
56		Omeprazole >< Glyceryl trinitrate	1	0.20
57		Omeprazole >< Isosorbide dinitrate	1	0.20
58		Omeprazole >< Nifedipine	1	0.20
59		Omeprazole >< Ciprofloxacin	1	0.20
60		Omeprazole >< Tocilizumab	1	0.20
61		Paracetamol >< Domperidone	1	0.20
62		Paracetamol >< Clidinium	1	0.20
63		Paracetamol >< Chloroquine	1	0.20
64		Ranitidine >< Sodium bicarbonate	1	0.20
	Total minor severity		**243**	**48.99**

The ACE2 protein, serving as the receptor for SARS-CoV-2, plays a critical role in this context. Notably, research measuring ACE2 protein expression in human cells has shown that Asian men exhibit higher levels of ACE2 expression compared to women. Furthermore, studies focusing on the expression of ACE2 in principal organs targeted by the virus have found that ACE2 expression in the lungs is more pronounced in Asian men than in women. Additionally, lifestyle factors, including smoking habits, alcohol consumption, and attitudes toward COVID-19 transmission prevention, differ significantly between genders and may contribute to these observed discrepancies (Bwire, 2020).

Hypertension was identified as the most common comorbidity among COVID-19 patients, followed by diabetes mellitus. Consistent with previous research, SARS-CoV-2 has been found to

precipitate more severe illness in individuals belonging to older age groups, as well as in those suffering from obesity, cardiovascular diseases, and diabetes (Bwire, 2020). Epidemiological and demographic analyses further underscore a heightened risk of COVID-19 among men, the elderly, individuals with pre-existing comorbidities, and those who have been in close contact with confirmed COVID-19 cases. The reduced efficacy of the immune system in older individuals may contribute to their increased susceptibility to infection. Moreover, chronic health conditions such as hypertension, diabetes, respiratory disorders, and cardiovascular diseases are believed to exacerbate the risk associated with COVID-19 (Shahbazi et al., 2020).

At Banyumas Hospital, the treatment protocol for COVID-19 patients includes the administration of corticosteroids, specifically dexamethasone and methylprednisolone. These corticosteroids are pivotal in mitigating inflammation, especially in severe or life-threatening cases (Noreen et al., 2021). Additionally, paracetamol, an analgesic and antipyretic, is used to alleviate fever, headache, and pain, providing symptomatic relief (Leal et al., 2021). The mucolytic agent N-acetylcysteine is also frequently prescribed. For the symptomatic management of gastrointestinal issues, medications such as omeprazole, ranitidine, and ondansetron are administered to address nausea, vomiting, and gastric distress.

Patients at risk of drug interactions are administered an average of five to six medications per instance. This observation underscores a direct correlation between the number of medications consumed and the probability of encountering drug interactions, with polypharmacy significantly contributing to this dynamic (Rahman and Bahar, 2020). Specifically, patients ingesting a higher number of medications—averaging nine—are observed to be four times more susceptible to adverse drug reactions compared to individuals who consume an average of five medications (Iloanusi et al., 2021).

Drug interactions during the pharmacokinetic phase can significantly alter drug levels, particularly affecting those with a narrow therapeutic index. Management strategies for these interactions vary depending on the phase in which they occur. During the absorption phase, implementing a temporal separation between drug administrations can mitigate interactions by adjusting the drug's residence time in the stomach. In the distribution phase, interactions may either increase or decrease the concentration of a drug at its action site, necessitating dose adjustments to maintain therapeutic efficacy. In the metabolism and excretion phase, drug interactions can alter the drug's elimination time, thereby extending or reducing the drug's presence in the body. To address these interactions, adjusting the dosage or temporarily halting the administration of one of the drugs until its elimination may be required. Furthermore, proactive measures to identify and minimize the risk of drug interactions across all pharmacokinetic phases are crucial (Ranieri, 2015; Synder et al., 2012).

This study investigated drug interactions characterized by pharmacokinetic mechanisms across the absorption, metabolism, and excretion phases. During the absorption phase, the interaction between paracetamol and metoclopramide was identified as having the highest probability of occurrence. Metoclopramide has been shown to increase the serum plasma concentration of paracetamol, accelerating the time it takes for paracetamol to reach its maximum concentration (Ragab, 2013). This interaction occurs as metoclopramide enhances the speed and rate at which drugs, including paracetamol, are absorbed in the small intestine by accelerating gastric emptying. It is recommended to closely monitor the patient's clinical condition and laboratory data to manage this drug interaction effectively, making dose adjustments as necessary (Preston, 2014).

During the metabolism phase, the combination of paracetamol and favipiravir presented the highest probability of drug interaction. Favipiravir is known to increase serum concentrations of paracetamol by inhibiting its metabolism. Paracetamol undergoes metabolism in the liver through three primary non-toxic pathways: glucuronidation, sulfation, and oxidative processes facilitated by cytochrome P450 enzymes. Favipiravir inhibits the sulfation pathway, impeding the conversion of paracetamol into its metabolite, paracetamol sulfate, consequently prolonging its presence in the body (Zhao et al., 2015). The resultant increased exposure necessitates a careful approach to managing this interaction. It is advisable to limit the daily intake of paracetamol to no more than three grams when co-administered with favipiravir to mitigate the risk of adverse effects (Lemaitre et al., 2020).

The analysis identified a significant likelihood of drug interaction between ranitidine and metformin during the absorption phase. Concurrent use of metformin with ranitidine may precipitate lactic acidosis, characterized by symptoms such as weakness, enhanced drowsiness, decelerated heart rate, muscular discomfort, respiratory difficulties, abdominal pain, dizziness, and episodes of fainting. The underlying mechanism involves ranitidine's capacity to obstruct the excretion of metformin by competing for renal tubular transport, thereby elevating metformin concentrations in the plasma. Ranitidine acts as a potent inhibitor of the multidrug and toxin extruder 1 (MATE1), significantly diminishing the renal clearance of metformin (Pakkir Maideen et al., 2017). In circumstances necessitating the co-administration of ranitidine and metformin, a reduced and more cautiously administered dose of metformin is recommended to mitigate the risk of this interaction. Moreover, it is imperative for patients to undergo periodic monitoring of their glycemic levels and to be vigilant for signs of lactic acidosis (Preston, 2014).

Observations have indicated potential synergistic interactions between dexamethasone and levofloxacin, highlighting an increased risk of tendon rupture associated with their concurrent use. Levofloxacin, when administered alongside corticosteroids like dexamethasone and methylprednisolone, may amplify this risk by diminishing the levels of critical tendon constituents. These include matrix protein type I, the transmembrane β1-integrin receptor, and the cytoskeleton protein vinculin, all of which are pivotal for the structural integrity and functionality of tendons. Similar interactions have been identified with other quinolones, such as moxifloxacin and ciprofloxacin, when combined with corticosteroids (Sendzik et al., 2010). Particularly vulnerable patient groups, including the elderly and recipients of kidney, heart, or lung transplants, are advised to cease the use of levofloxacin, abstain from strenuous physical activity, and remain vigilant for symptoms such as pain, swelling, or signs of tendonitis.

The combination of paracetamol and ondansetron has been identified as having the highest incidence of potential pharmacodynamic antagonistic interactions. Ondansetron, functioning as a 5-HT3 antagonist, possesses antiemetic properties that may compromise the analgesic effectiveness of paracetamol. Paracetamol's analgesic action involves the stimulation of serotonergic receptors, particularly 5-HT3 receptors. Consequently, the simultaneous administration of paracetamol and ondansetron could reduce paracetamol's pain-relieving capacity. In scenarios where the concurrent use of these drugs is unavoidable, adjusting the dosage may serve as an effective strategy for managing this potential drug interaction (Bhosale et al., 2014).

The triad interaction among ondansetron, hydroxychloroquine, and moxifloxacin has been identified as a means of induced QT interval prolongation. Prolonging the QT interval, resulting from the blockade of potassium ion channels, extends the repolarization duration, potentially leading to an elevated heart rate (Nachimuthu et al., 2012). The coadministration of these drugs, each capable of prolonging the QT interval, may synergistically amplify the risk of arrhythmogenic events due to their additive effects. Consequently, exercising caution by avoiding the concurrent use of these medications while ensuring close monitoring of the QT interval, electrolyte imbalances, and renal function is imperative (McKechnie and Froese, 2010).

Drug interactions are stratified into minor, moderate, and major categories based on their severity, with each category necessitating a tailored management approach. Minor severity interactions are considered to have negligible clinical impact or a low risk of significant side effects, thus not warranting specific management measures. On the other hand, moderate-severity interactions could worsen the patient's condition, requiring strategies aimed at risk minimization. These strategies encompass rigorous monitoring of the therapeutic regimen to evaluate its efficacy, detect adverse drug reactions, and observe other relevant physiological parameters. There may also be a need for therapy alteration or adjustments in the drug's administration, including changes to dosage, treatment duration, and timing of administration (Lexicomp Drug Interaction Analysis, 2023; Shariff et al., 2022).

In contrast, major severity interactions pose a significant risk to the patient's life or could inflict permanent damage. In such cases, it is critical to discontinue the implicated drug(s). An example of a potential drug interaction classified as major involves the concomitant use of ondansetron with hydroxychloroquine and moxifloxacin, a combination known to elevate the risk of arrhythmias due to QT interval prolongation.

Our study is limited by its focus on potential and theoretical drug interactions, leaving the actual occurrence of these interactions in a clinical setting to be determined. Prospective studies are necessary to evaluate the real-world incidence of drug interactions by observing clinical manifestations in patients.

CONCLUSION

The investigation reveals a widespread potential for drug interactions among COVID-19 patients, particularly those prescribed corticosteroids and symptomatic medications. However, it is crucial to note that not all identified drug interactions may result in clinically significant outcomes. Consequently, there is an urgent need for further empirical research to explore the extent of potential drug-drug interactions comprehensively and to develop strategies for mitigating the risk of adverse effects stemming from such interactions.

ACKNOWLEDGMENTS

Thanks to Nia Kurnia Solihat and Masita Wulandari for providing feedback on the manuscript. We appreciate Jenderal Soedirman University for funding this research through the UNSOED 2021 Basic Research Grant T/654/UN23.18/PT.01.03/2021.

CONFLICT OF INTEREST

No conflict of interest

REFERENCES

Ahmad, S., Ali, S., Alam, N., Alam, I., Alam, S., Ali, D., 2016. Drug interactions of H2 receptor antagonists-ranitidine: a review. *Research Journal of Pharmacy and Technology* 9(2), 275. https://doi.org/10.5958/0974-360X.2016.00051.2

Bayat, V., Ryono, R., Phelps, S., Geis, E., Sedghi, F., Etminani, P., Holodniy, M., 2021. Reduced mortality with ondansetron use in SARS-CoV-2-infected inpatients. *Open Forum Infectious Diseases* 8(10), ofab336. https://doi.org/10.1093/ofid/ofab336

Bhosale, U.A., Khobragade, R., Naik, C., Yegnanarayan, R., Kale, J., 2014. Postoperative pharmacodynamic interaction of ondansetron; a 5-HT3 antagonist and paracetamol in patients operated in the ENT department under local anesthesia. *Journal of Basic and Clinical Pharmacy* 5(3), 84–86. https://doi.org/10.4103/0976-0105.139732

Bwire, G.M., 2020. Coronavirus: why men are more vulnerable to Covid-19 than women? *SN Comprehensive Clinical Medicine* 2(7), 874–876. https://doi.org/10.1007/s42399-020-00341-w

Gavriatopoulou, M., Ntanasis-Stathopoulos, I., Korompoki, E., Fotiou, D., Migkou, M., Tzanninis, I.-G., Psaltopoulou, T., Kastritis, E., Terpos, E., Dimopoulos, M.A., 2021. Emerging treatment strategies for COVID-19 infection. *Clinical and Experimental Medicine* 21(1), 167–179. https://doi.org/10.1007/s10238-020-00671-y

Gibson, P.G., Qin, L., Puah, S.H., 2020. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *Medical Journal of Australia* 213(2), 54–56.e1. https://doi.org/10.5694/mja2.50674

Hodge, C., Marra, F., Marzolini, C., Boyle, A., Gibbons, S., Siccardi, M., Burger, D., Back, D., Khoo, S., 2020. Drug interactions: a review of the unseen danger of experimental COVID-19 therapies. *Journal of Antimicrobial Chemotherapy* 75(12), 3417–3424. https://doi.org/10.1093/jac/dkaa340

Iloanusi, S., Mgbere, O., Essien, E.J., 2021. Polypharmacy among COVID-19 patients: A systematic review. *Journal of the American Pharmacists Association* 61(4), e14–e25. https://doi.org/10.1016/j.japh.2021.05.006

Lai, C.-C., Shih, T.-P., Ko, W.-C., Tang, H.-J., Hsueh, P.-R., 2020. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. International *Journal of Antimicrobial Agents* 55(3), 105924. https://doi.org/10.1016/j.ijantimicag.2020.105924

Leal, N.S., Yu, Y., Chen, Y., Fedele, G., Martins, L.M., 2021. Paracetamol is associated with a lower risk of COVID-19 infection and decreased ACE2 protein expression: a retrospective analysis. *COVID* 1(1), 218–229. https://doi.org/10.3390/covid1010018

Lemaitre, F., Solas, C., Grégoire, M., Lagarce, L., Elens, L., Polard, E., Saint-Salvi, B., Sommet, A., Tod, M., Barin-Le Guellec, C., French Society of Pharmacology, Therapeutics

(SFPT), International Association of Therapeutic Drug Monitoring, Clinical Toxicology (IATDMCT), 2020. Potential drug-drug interactions associated with drugs currently proposed for COVID-19 treatment in patients receiving other treatments. *Fundamental & Clinical Pharmacology* 34(5), 530–547. https://doi.org/10.1111/fcp.12586

Lexicomp Drug Interactions Analysis [WWW Document], 2023. URL https://www.wolterskluwer.com/en/solutions/lexicomp/resources/lexicomp-user-academy/drug-interactions-analysis (accessed 2023-06-10).

Mattos-Silva, P., Felix, N.S., Silva, P.L., Robba, C., Battaglini, D., Pelosi, P., Rocco, P.R.M., Cruz, F.F., 2020. Pros and cons of corticosteroid therapy for COVID-19 patients. *Respiratory Physiology & Neurobiology* 280, 103492. https://doi.org/10.1016/j.resp.2020.103492

McKechnie, K., Froese, A., 2010. Ventricular tachycardia after ondansetron administration in a child with undiagnosed long QT syndrome. *Canadian Journal of Anesthesia* 57(5), 453–457. https://doi.org/10.1007/s12630-010-9288-2

Meng, X., Deng, Y., Dai, Z., Meng, Z., 2020. COVID-19 and anosmia: A review based on up-to-date knowledge. American *Journal of Otolaryngology* 41(6), 102581. https://doi.org/10.1016/j.amjoto.2020.102581

Nachimuthu, S., Assar, M.D., Schussler, J.M., 2012. Drug-induced QT interval prolongation: mechanisms and clinical management. *Therapeutic Advances in Drug Safety* 3(5), 241–253. https://doi.org/10.1177/2042098612454283

Nawawi, M.I., Pathuddin, H., Masrifah, R., 2021. Description of the relationship between gender and patients status of covid-19 in Indonesia. *Jukema* 7(1), 76–81. https://doi.org/10.37598/jukema.v7i1.1069

Noreen, S., Maqbool, I., Madni, A., 2021. Dexamethasone: Therapeutic potential, risks, and future projection during COVID-19 pandemic. *European Journal of Pharmacology* 894, 173854. https://doi.org/10.1016/j.ejphar.2021.173854

Pakkir Maideen, N.M., Jumale, A., Balasubramaniam, R., 2017. Drug interactions of metformin involving drug transporter proteins. *Advanced Pharmaceutical Bulletin* 7(3), 501–505. https://doi.org/10.15171/apb.2017.062

Preston, C.L. (Ed.), 2014. Stockley's Drug Interactions Pocket Companion 2014, Revised edition. *Pharmaceutical Press*.

Ragab, M.A.A., 2013. Effect of metoclopramide on the excretion rate of paracetamol using HPLC-DAD. *Journal of Chromatographic Science* 51(5), 383–390. https://doi.org/10.1093/chromsci/bms152

Rahman, S., Bahar, T., 2020. COVID-19: The new threat. *International Journal of Infection* 7(1), Article e102184. https://doi.org/10.5812/iji.102184

Ranieri, M., 2015. Casebook in clinical pharmacokinetics and drug dosing. *American Journal of Health-System Pharmacy* 72(14), 1238–1239. https://doi.org/10.1093/ajhp/72.14.1238a

Ray, A., Sharma, S., Sadasivam, B., 2020. The potential therapeutic role of proton pump inhibitors in COVID-19: hypotheses based on existing evidences. *Drug Research* 70(7), 484–488. https://doi.org/10.1055/a-1236-3041

Rezaee, H., Pourkarim, F., Pourtaghi-Anvarian, S., Entezari-Maleki, T., Asvadi-Kermani, T., Nouri-Vaskeh, M., 2021. Drug-drug interactions with candidate medications used for COVID-19 treatment: An overview. *Pharmacology Research & Perspectives* 9(3), e00705. https://doi.org/10.1002/prp2.705

Sendzik, J., Shakibaei, M., Schäfer-Korting, M., Lode, H., Stahlmann, R., 2010. Synergistic effects of dexamethasone and quinolones on human-derived tendon cells. *International Journal of Antimicrobial Agents* 35(4), 366–374. https://doi.org/10.1016/j.ijantimicag.2009.10.009

Shahbazi, F., Solgi, M., Khazaei, S., 2020. Predisposing risk factors for COVID-19 infection: A case-control study. *Caspian Journal of Internal Medicine* 11(4), 495–500. https://doi.org/10.22088/cjim.11.0.495

Shariff, A., Belagodu Sridhar, S., Abdullah Basha, N., Bin Thaleth Alshemeili, S.S.H., Ahmed Aljallaf Alzaabi, N.A., 2022. Development and

validation of standardized severity rating scale to assess the consistency of drug-drug interaction severity among various drug information resources. *Research in Social and Administrative Pharmacy* 18(9), 3323–3328. https://doi.org/10.1016/j.sapharm.2021.12.006

Snyder, B.D., Polasek, T.M., Doogue, M.P., 2012. Drug interactions: principles and practice. *Australian Prescriber* 35(1), 12–15. https://doi.org/10.18773/austprescr.2012.037

WHO, 2022. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. https://covid19.who.int/

Zhao, Y., Harmatz, J.S., Epstein, C.R., Nakagawa, Y., Kurosaki, C., Nakamura, T., Kadota, T., Giesing, D., Court, M.H., Greenblatt, D.J., 2015. Favipiravir inhibits acetaminophen sulfate formation but minimally affects systemic pharmacokinetics of acetaminophen. *British Journal of Clinical Pharmacology* 80(6), 1076–1085. https://doi.org/10.1111/bcp.12644