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Drug Interaction of Covid-19 In Intensive Care Unit Patients In South Kalimantan, Indonesia

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Abstract: A drug interaction is a pharmacological or clinical response to the administration of two or more drugs that differs from the response. One of the risk factors for drug interactions is patients in ICU care so that they are at greater risk for drug interactions. Often drug interactions are unknown in patients so it is important to investigate COVID-19 drug interactions especially in ICU patients because there are very few studies available thereby increasing patient safety in hospital ICU care. This study was conducted retrospectively by cross-sectional observational analytic to look at the drug interactions of COVID-19 in ICU patients in May - October 2020. This study was conducted at one of the Hospitals that has ICU facilities for COVID-19. Drugs prescribed during the patient's hospitalization were evaluated for drug interactions using the drugs.com Data were taken from 68 patients with a total of 1020 prescriptions. Based on this number, 196 types of interactions were identified, consisting of 16.84% major, 71.94% moderate and 11.22% minor. Based on the results of research, drug interactions that often occur in ICU-COVID patients in South Kalimantan are lopinavir/ritonavir with colchicine, lopinavir/ritonavir with midazolam and lopinavir/ritonavir with hydroxychloroquine.

Keyword: Drug Interaction, COVID-19, Intensive Care Unit

I. INTRODUCTION

A drug interaction is a pharmacological or clinical response to the administration of two or more drugs that differs from the response [1].These interactions can cause the effect of the drug to be reduced, zero, or increased. Risk factors that contribute to drug interactions include patients receiving intensive care, immunosuppressed patients, patients with complex clinical conditions requiring large amounts of prescription drugs with long duration of hospital stay, and increased health care costs[2]. The above risk factors relate to patients in ICU care so that they are at greater risk for drug interactions. A study conducted in the ICU showed that the risk of drug interactions increased by about 6% per day. Often drug interactions go unnoticed in these patients as their symptoms are due to disease [3].

COVID-19 is the name given to the disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2¨ (SARS-CoV-2), which was officially declared a global pandemic by the World Health Organization (WHO). Currently, there is no specific treatment for COVID-19. Treatment recommendations by the Ministry of Health are given in accordance with currently available drugs (hydroxychloroquine, Azithromycinromycin, oseltamivir, lopinavir/ritonavir, favipiravir and remdesivir) in Indonesia. All of these drugs have many potential drug interactions that differ in clinical significance and are metabolized in the liver [4]. Beside from other organ dysfunctions, acute kidney injury and liver dysfunction have also been reported in COVID-19 patients which may affect the severity of drug-drug interactions and drug side effects due to pharmacokinetic changes [5].Based on this, it is important to investigate the drug interactions of COVID-19 especially in ICU patients because there are very few studies available thereby increasing patient safety in hospital ICU care.

II. MATERIALS AND METHODS

This study design was a descriptive cross-sectional study with retrospective data collection from May to October 2020. The inclusion criteria were ICU inpatients with a diagnosis of COVID-19 and receiving COVID-19 therapy. Exclusion criteria were patients who met the inclusion criteria would be excluded from the study if they received less than two drugs. The diagnosis of COVID-19 was confirmed by positive PCR in a nasopharyngeal swab sample. Data on prescribed drugs were collected using patient prescription records.

This study has been approved by the Hospital Ethics Committee (No. 13/III-Reg Studi/RSUDU/21) which has been carried out with local ethical considerations. All patient information confidentiality and security is provided with limited access to investigators.

Information was collected using the website http://www.drugs.com/drug_interactions through smartphone software so that the types of interactions between the drugs were obtained. The severity of drug interactions can be classified into three types namely: 'Major' interaction if the interaction can endanger the patient's life or cause permanent damage, 'Moderate' interaction if the interaction can cause damage to the patient's clinical condition, leading to additional treatment or prolongation of the period. hospital stay and 'Minor' interactions if interactions are small, undetectable, or predictable, and without clinically significant involvement.

The data is recorded in a Microsoft Office Excel file. Descriptive statistics were used to analyze the demo graph of the total characteristics of drug interactions with drugs.com Values are presented as numbers and percentages as appropriate.

III. RESULTS AND DISCUSSION

The results of the study from ICU-COVID patients in May - October 2020 found 68 patients with the average number of drugs per patient being more than 15 types of drugs, both injection and oral drugs. So the total number of recipes is 1020 the number of recipes. Based on this number, 196 types of interactions were obtained and the total of all were 905 interactions. The results are divided into 3 categories based on the degree of severity, namely major, moderate and minor, which can be seen in Table 1.

Drug interactions are possible in patients with multitherapy or polypharmacy. Drug interactions in the body can occur in various reactions either through absorption, distribution, metabolism and excretion of all drugs involved. This process has the potential to trigger and inhibit enzymes and transporters, interactions will also affect bioavailability, protein generation and hepatic/kidney excretion. [6]. Based on the results of the study, it is known that the incidence of drug interactions is 33 major(16,84 %), 141 moderate (71,94%) dan 77 minor (11,22%).

Table 1. Result Drug Interaction

Classification of Drug Interaction	Total	Total	Type interaction		
Mayor	33	215	1	lopinavir/ritonavir + Colchicine	8,84%
			2	lopinavir/ritonavir + Midazolam	8,84%
			3	Azithromycin +Hydroxycloroquin	8,84%
			4	lopinavir/ritonavir + Ator	6,98%
			5	lopinavir/ritonavir +Hydroxycloroquin	5,58%
Moderate	141	613	1	lopinavir/ritonavir +Exjade	2,77%
			2	lopinavir/ritonavir +Levo	2,77%
			3	lopinavir/ritonavir + Fluco	2,77%
			4	lopinavir/ritonavir +Dexa	2,45%
			5	lopinavir/ritonavir + Azithromycin	2,45%
Minor	22	77	1	Aspirin +Lanso	10,39%
			2	CPG + Heparin	10,39%
			3	Bricasma + MP	9,09%
			4	MP + Zink	9,09%
			5	MP + Midazolam	6,49%

The drug that interacts the most is the drug combination lopinavir/ritonavir. The most major interactions were the combination of lopinavir/ritonavir + Colchicine, Lotinavir/ritonavir + Midazolam and Azithromycin + Hydroxychloroquine. lopinavir/ritonavir + Colchicine is used concurrently for the treatment of COVID-19. Colcicine is used in the treatment of acute pericarditis but in COVID patients it is used as an adjunct therapy because of its anti-inflammatory effect. This effect interferes with several anti-inflammatory pathways including neutrophil adhesion and recruitment, superoxide production, inflammatory activation and TNF- release. The tubulin complex of colcine affects the microtubules that play a role in the entry, transportation and replication of the corona virus [7]. Concomitant administration significantly increased the maximal concentration and AUC of colchicine[8].

Lopinavir/ritonavir + Midazolam is used concurrently as an antiviral and sedation in Covid ICU patients. These patients require sedation and analgesics because the Corona virus binds to the angiotensin converting enzyme II receptor which is expressed in the lower respiratory tract causing increased production of angiotensin II. This increase leads to pulmonary vascular permeability and the induction of cytokines [9]. This then leads to endothelial injury leading to complications from pneumonia, acute respiratory distress syndrome and severe acute hypoxic respiratory failure requiring invasive mechanical ventilation requiring effective and appropriate sedation and analgesics[10]. Midazolam is a class of benzodiazepine drugs that have GABA activity which provides effects, especially sedation, amnesia, anticonvulsants and muscle relaxation. Concomitant use of lopinavir/ritonavir with midazolam can cause protease inhibitors thereby increasing serum midazolam concentrations [11].

Azithromycin and Hydroxychloroquine used together may prolong the QT interval and may cause additive effects and an increased risk of ventricular arrhythmias including torsade de pointes and sudden death.[12]**.** Azithromycin has been shown to be active in vitro against Zika and Ebola viruses and to prevent severe respiratory tract infections in patients with viral infections. Another study also showed that concomitant Hydroxychloroquine treatment with Azithromycin was significantly associated with a reduction in viral progression in COVID patients[8].

Moderate interactions are interactions that only need to monitor the use of the interacting drug. The results of this study showed that the top 5 moderate interactions were the combination of lopinavir/ritonavir. Lopinavir/ritonavir is an anti-HIV drug used as an antiviral for COVID-19 therapy. It inhibits CYP3A as well as several major transporters of P-gp, BCRP and OATP1B1. Many drugs interact because the majority of drugs go through this route. It also has the potential to reduce exposure to some drugs metabolized by CYP enzymes (CYP1A2, CYP2B6, CYP2C9, CYP2C19) and glucuronidation. In addition, this drug also has the effect of prolonging the QT interval[13]. Minor interactions require neither special monitoring nor significant influence.

IV. CONCLUSIONS

Drug interactions that often occur in COVID ICU patients in South Kalimantan are lopinavir/ritonavir with colcine, lopinavir/ritonavir with midazolam and lopinavir/ritonavir with hydroxychloroquine.

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