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RELEVANT DRUG INTERACTIONS BETWEEN DRUGS THAT ACT ON THE CENTRAL NERVOUS SYSTEM AND DRUGS USED TO TREAT COVID-19

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Abstract: The disease caused by the virus: *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) It is a pathology with a clinical picture that varies from asymptomatic infections to severe respiratory conditions. Antiretroviral, antimalarial and antiparasitic drugs are being studied for the treatment of COVID-19 and its complications, due to their mechanism of action. However, most actions and interventions are empirical and derived from in vitro tests. Thus, it is important to evaluate drug interactions (DIs) in order to promote greater effectiveness and safety of therapy. Taking into consideration, the increase in the use of drugs that act on the central nervous system (CNS) during the pandemic, due to the increase in mental disorders, one of the biggest public health problems worldwide, the present study aimed to identify the potential drug interactions of these drugs. main drugs used in the treatment of COVID-19 in association with drugs that act on the CNS, standardized in a University Hospital in Sergipe. For that, the following databases were used: MedScape, UpToDate and Drugs, selecting the interactions classified as moderate and severe severity, exposing the possible complications. After analysis, 77 interactions were observed, of which 56 were of moderate severity and 21 were severe, highlighting the drugs atazanavir, lopinavir/ritonavir and hydroxychloroquine/chloroquine for interacting with a greater number of drugs. Given this context, it is necessary for prescribers and dispensers to be aware of the risks of concomitant administration of these classes, in addition to monitoring the consequences, evaluating patient safety in the face of the use of these drugs.

Keywords: COVID-19, drug interaction, patient safety.

INTRODUCTION

COVID-19 is a respiratory illness caused by the virus *severe acute respiratory syndrome coronavirus* 2 (SARS-CoV-2), also known as novel coronavirus, which presents a clinical picture that varies from asymptomatic infections to severe respiratory conditions and/or severe pneumonia (MCINTOSH, et al., 2020). According to the World Health Organization (WHO), in 2021, most patients with COVID-19 (about 80%) were asymptomatic, and only about 20% resorted to hospital care, of which about 5 % required ventilatory support. The transmission of the virus occurs mainly with the contact of respiratory droplets from sick, symptomatic and asymptomatic patients [1].

In the scenario of a pandemic, most actions and interventions are empirical and based on findings derived from in vitro experiments, as well as informal personal experiences and small observational studies without adequate methodology. However, such a process can lead to irrational self-medication, excess secondary treatment that associated with the use of drugs without an approved therapeutic indication to combat COVID-19 can generate serious adverse events [2].

In order to achieve promising results in the control of COVID-19, drugs such as antiparasitics, antivirals and antimalarials are being evaluated. Antivirals, for example, are among the most promising in the fight against SARS-CoV-2, with emphasis on remdesevir, a broad-spectrum antiviral, which is related to the reduction of viral load in vitro. Favipiravir is related to selective inhibition of viral RNA-dependent RNA polymerase [3,4]. And lopinavir/ritonavir which is an antiretroviral agent that acts by inhibiting the HIV protease and has shown to reduce the viral load of SARS-CoV-2 in vitro [5].

Regarding antiparasitic agents, in vitro studies have shown positive results against

infection caused by SARS-CoV-2. Ivermectin, at a higher dosage than that used in parasitic therapy, reduced the RNA of the new coronavirus. However, the use of this drug lacks evidence in a clinical environment, effectiveness and safety tests [6]. Nitazoxanide, according to an in vitro study, has an inhibitory capacity against SARS-CoV-2 at a low micromolar concentration. However, an additional in vivo assessment against infection caused by the novel coronavirus is recommended [3].

Other strategies initially used in the treatment and prevention of infection caused by SARS-CoV-2 were chloroquine and its analogue hydroxychloroquine, which showed a reduction in mortality and the need for mechanical ventilation [7]. However, the available scientific evidence related to the use of these drugs in the fight against SARS-CoV-2 was considered inconclusive and insufficient [8]. The Brazilian Society of Immunology advises that it is still too early to recommend the use of these drugs, since different studies have shown that there were no benefits for patients [9].

Thus, it is worth emphasizing the importance of evaluating potential and actual drug interactions (DIs), since both the identification and prevention of these interactions are directly related to the effectiveness and safety of drug therapy. The identifications of drug interactions, in turn, are among the main interventions carried out by the Clinical Pharmacy in the care of patients in intensive care in COVID-19. In this sense, the inclusion of the pharmacist in the health team has contributed to the improvement and adequacy of the medical prescription, increasing the safety and quality of care provided to the patient [10]. Thus, during the selection of pharmacological therapy for the treatment of COVID-19, it is extremely important to consider the role of the clinical pharmacist in the evaluation of possible drug interactions between the drugs selected for the treatment of COVID-19 and the other drugs used by patients.

Taking into account the increased use of drugs that act on the central nervous system during the pandemic, due to the increase in mental disorders [11], and for being one of the biggest public health problems worldwide, considering the magnitude and diversity of the aspects involved [12], the present study aimed to identify the potential drug interactions of the main drugs used in the treatment of COVID-19 in association with drugs that act on the central nervous system, standardized in a University Hospital in Sergipe.

MATERIAL AND METHODS

Based on the drugs mentioned for the treatment of COVID, atazanavir, lopinavir/ritonavir, remdesivir, chloroquine, hydroxychloroquine, nitazoxamide and ivermectin, and the drugs that act on the central nervous system belonging to the list of standardized drugs of the Hospital Universitário de Lagarto, from the Federal University de Sergipe (HUL-UFS), a survey of drug interactions between them was carried out.

The HUL-UFS is part of the process of expansion and internalization of the UFS to meet the health needs of the population of Lagarto and region. Opened in 2010, it meets the training demands of students at the University Campus of Lagarto, which offers courses in Medicine, Dentistry, Nursing, Physiotherapy, Pharmacy, Speech Therapy, Nutrition and Occupational Therapy, as well as a multi-professional and medical residency comprising the same courses, except for the dentistry course. The HUL-UFS provides care to patients of various age groups, with a capacity of 94 beds and 24-hour emergency care. The beds are distributed as follows:

12 intensive care beds, 63 ward beds and 19 emergency urgency unit beds, with care focused mainly on the specialties of internal medicine, orthopedics and traumatology, nutrition, pediatrics, general surgery, surgery pediatrics and laboratory tests. In addition to the beds of the Respiratory Unit (part directed to COVID-19) which has its quantity oscillating, according to the demand and incidence of the virus.

To evaluate drug interactions, the UpToDate and DRUGS databases were used. These bases were used to search for information about possible interactions, from their severity to the consequences caused in the body.

The interactions selected were those of moderate and severe severity. In addition, data searches were also carried out in scientific articles, case reports and clinical trials, to elucidate the mechanisms involved in possible interactions, as well as to assess the safety of these drugs.

RESULTS AND DISCUSSION

Among the 367 standardized drugs at the institution, 32 were selected that act on the central nervous system, being compared with the eight drugs that are under evaluation and those that were evaluated as a possible treatment for COVID-19. After analyzing 256 comparisons, it was observed that 175 do not have drug interactions with each other and four have drug interactions with mild severity, requiring only monitoring. Furthermore, 77 interactions were observed, of which 56 were of moderate severity (72.7%) and 21 were severe (27.2%), which could endanger the patient's life.

Table 1 shows all drugs that had relevant drug interactions (in orange and red) and the severity of these interactions. Some drugs such as atazanavir, lopinavir/ritonavir and hydroxychloroquine/chloroquine interacted with a greater number of drugs (75%; n=24). While other drugs such as remdesivir, nitazoxamide and ivermectin interacted with a smaller number of drugs (18.7%; n=6); favipiravir did not interact with any drug evaluated.

After analysis and comparisons between drugs that act on the central nervous system and drugs used for COVID-19, it was possible to observe that there are different types and severities of associated DIs. In the daily practice of services, the correct diagnosis of these problems requires the skill and experience of the multidisciplinary team [13], especially in conjunction with the clinical pharmacist. Recent studies show that pharmaceutical interventions with physicians represented a 66% decrease in preventable adverse events [14]. In this study, most associations did not present drug interactions between drugs; however, the presence of interactions classified as moderate and severe was observed and, as these are clinically significant interactions, whose combinations must be avoided, it is necessary to highlight the clinical importance that must be given to them in drug therapy.

Atazanavir, an antiretroviral agent of the protease inhibitor class, indicated in combination with other antiretroviral agents for the treatment of HIV infection [15], has been studied as a possible treatment for COVID-19. It was found that this drug has good results on SARS-CoV-2 in studies with cells in the laboratory, being able to inhibit viral replication; in addition to reducing the production of proteins that are linked to the inflammatory process in the lungs and, therefore, to the worsening of the clinical picture of the disease [16].

However, when analyzing it being administered concomitantly with general anesthetics (alfentanil, fentanyl and ketamine), anxiolytics (alprazolam, midazolam and diazepam), antipsychotics (haloperidol and quetiapine) and antidepressants

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	NITA	IVER
GENERAL ANESTHETICS								
Alfentanil	■	●	◆	◆	◆	◆	◆	◆
Ketamine	■	■	◆	◆	◆	◆	◆	◆
Dexmedetomidine	◆	◆	◆	◆	◆	◆	◆	◆
Etomidate	◆	◆	◆	◆	◆	◆	◆	◆
Fentanyl	■	●	◆	◆	◆	◆	◆	◆
Isoflurane	◆	◆	◆	◆	◆	◆	◆	◆
Propofol	◆	■	◆	◆	■	■	◆	◆
Remifentanil	◆	◆	◆	◆	◆	◆	◆	◆
Sevoflurane	◆	■	◆	◆	■	■	◆	◆
ANTICONVULSANTS								
Valproic acid	◆	■	◆	◆	◆	◆	■	◆
Carbamazepine	●	●	■	◆	●	●	◆	■
Clonazepam	■	■	◆	◆	◆	◆	◆	◆
Phenytoin	■	●	■	◆	●	●	■	■
Phenobarbital	■	●	■	◆	●	●	◆	◆
magnesium sulfate	◆	◆	◆	◆	◆	◆	◆	◆
Topiramate	◆	◆	◆	◆	◆	◆	◆	◆
ANXIOLYTICS								
Alprazolam	■	■	◆	◆	◆	◆	◆	◆
Diazepam	■	■	◆	◆	◆	◆	■	◆
Midazolam	●	●	◆	◆	◆	◆	■	◆
ANTIPARKINSONIAN								
biperiden	◆	◆	◆	◆	◆	◆	◆	◆
ANTIPSYCHOTICS								
Chlorpromazine	◆	■	◆	◆	■	■	◆	◆
Clozapine	◆	●	◆	◆	●	●	◆	◆
Haloperidol	■	●	◆	◆	■	■	◆	◆
Levomepromazine	◆	●	◆	◆	■	■	◆	◆
Quetiapine	●	●	◆	◆	■	■	◆	◆
Risperidone	◆	■	◆	◆	■	■	◆	◆
ANTIDEPRESSANTS								
Amitriptyline	■	■	◆	◆	■	■	◆	◆
Citalopram	■	■	◆	◆	■	■	◆	◆
Escitalopram	■	■	◆	◆	■	■	◆	◆
Fluoxetine	◆	◆	◆	◆	■	■	◆	◆
Sertraline	◆	■	◆	◆	◆	◆	◆	◆
Venlafaxine	◆	◆	◆	◆	◆	◆	◆	◆

Table 1: Main drug interactions involving the drugs planned for the treatment of COVID-19 and the standardized HUL-UFS.

ATV	Atazanavir	CLQ	chloroquine
LPV/r	Lopinavir/ritonavir	HCLQ	Hydroxychloroquine
RDV	Remdesivir	NTA	Nitazoxanide
FAVI	Favipiravir	IVER	ivermectin

Table 2: Abbreviations.

•	Severe Severity – Avoid combination
▪	Moderate Severity – Consider therapy modification
◆	Mild Severity - Monitor therapy
◆	No interactions were identified

Table 3: Symbols.

(amitriptyline, citalopram, escitalopram and sertraline) it was observed that atazanavir may increase the bioavailability of psychotropic drugs, and consequently, lead to possible side effects. Already with anticonvulsants, (carbamazepine, clonazepam, phenytoin and phenobarbital) can reduce the blood levels of atazanavir, resulting in a decrease in the effectiveness of the treatment.

Lopinavir/ritonavir, an antiretroviral agent that acts by inhibiting HIV protease, is another one considered to be relatively safe in its short-term use, but due to the limited number of patients evaluated, it is still not considered beneficial in the treatment of infection caused by SARS. -CoV-2, therefore, it is necessary to carry out randomized control studies [10, 17]. When evaluating interactions, it was observed that lopinavir/ritonavir may result in an increase in blood levels of the following drugs: alfentanil, fentanyl, ketamine, proprofol, sevoflurane, alprazolam, midazolam, diazepam, chlorpromazine, clozapine, haloperidol, levomepromazine, quetiapine, risperidone, amitriptyline, citalopram, escitalopram and clonazepam. On the other hand, anticonvulsants such as carbamazepine, phenytoin and phenobarbital can decrease blood levels of LPV/R, which can make it less effective in treatment.

Regarding remdesivir, a prodrug initially developed as a treatment for Ebola virus disease, which acts by incorporating the viral RNA polymerase chain, aiming to interrupt the viral genome replication process, it has shown to be promising for the treatment of COVID-19 [3, 18]. When analyzing drug interactions, a risk of decreased absorption of this drug was noted when administered concomitantly with carbamazepine, phenytoin and phenobarbital.

Favipiravir - a prodrug that has action against several viruses, such as influenza, yellow fever, foot-and-mouth disease, among others - was suggested as a treatment for COVID-19 due to its activity against the RNA of the virus. However, there are still no studies that prove such effectiveness. Due to its pharmacodynamics, the drug molecule can inhibit some CYP families, which may potentiate the action of some co-administered drugs [21]. However, it did not show any drug interactions when used in conjunction with the class that acts on the CNS.

Hydrochloroquine and chloroquine - drugs used as prophylaxis and treatment of malaria, hepatic amebiasis, rheumatoid arthritis, systemic lupus erythematosus and

discoid lupus, among other pathologies - in the COVID-19 pandemic, were studied due to their possible ability to inhibit replication of the virus, after results of studies observed in vitro. It was observed that the ability to interfere with virus infection and replication is related to the increase in endosomal pH, blocking the transport of SARS-CoV-2 between cell organelles (endosomes and endolysosomes). In addition, there are studies that cite the ability of this drug to interact with the angiotensin-converting enzyme 2 (ACE2) and in the terminal glycosylation of the ACE2 cellular receptor, inhibiting the binding of the virus to the receptor and, consequently, its infection [6, 8], 22].

When analyzing interactions, increased concentrations in blood levels and possible adverse reactions were noted in the following drugs: propofol and sevoflurane (general anesthetics); amitriptyline, citalopram, escitalopram (antidepressants); chlorpromazine, haloperidol, levomepromazine, quetiapine and risperidone (antipsychotics). In the case of clozapine, it was observed that when administered together with hydrochloroquine and chloroquine, agranulocytosis can develop, while anticonvulsants (carbamazepine, phenytoin and phenobarbital) can decrease the bioavailability of hydrochloroquine and chloroquine and, consequently, lead to a possible therapeutic failure.

Another drug evaluated was nitazoxanide, an antimicrobial agent with a broad spectrum of action, which has activity against species of protozoa and helminths, which began to be studied for the treatment of COVID-19 because it is believed that this drug has an antiviral action through inhibition of synthesis of the viral structure called protein 7 in its interaction with the cell, blocking the ability of the virus to replicate itself [23, 24]. When administering this antimicrobial together with drugs that act on the CNS, there is interaction only with anticonvulsants (valproic acid and phenytoin) and anxiolytics (midazolam and diazepam), being able to cause an increase in blood levels of anticonvulsants and anxiolytics.

Ivermectin is an effective and potent antiparasitic drug that acts against several species of parasites [25] and, taking into account previous trials, was tested on cells infected with SARS-Cov2 [5, 21]. When investigating IMs, it was found that carbamazepine and phenytoin (P-glycoprotein inhibitors) can decrease the serum concentration of ivermectin, directly affecting the therapeutic effects of the drug.

It is worth emphasizing that the increase in blood concentration of general anesthetics can result in more frequent systemic toxicity reactions such as cardiotoxicity, neurotoxicity, hematotoxicity; in addition to increasing the risk of an irregular heart rhythm [19]. Anxiolytics have side effects such as excessive sedation, respiratory depression, low blood pressure and irregular heart rhythm. Antipsychotics and antidepressants can cause dizziness, drowsiness, dry mouth, constipation, increased appetite, weight gain, hyperglycemia, hyperdyslipidemia, among others. In general, psychotropic drugs usually produce adverse effects, mainly anticholinergic, dopaminergic, histaminergic and adrenergic effects. Some side effects are transient and usually last only in the initial weeks of treatment during the drug adaptation phase (nausea, headache, dizziness), while others are long-lasting and permanent (weight gain, sexual dysfunction, extrapyramidal symptoms) [20]. Thus, when having increased concentrations in the body, the probability of developing such adverse effects is greater.

It is important to highlight that the identification of DIs detects possible changes in the pharmacokinetics and/or pharmacodynamics of the drugs, which may develop complications; however, it does not

mean that the adverse events described in this study will manifest clinically. To recognize and diagnose this undesirable outcome, healthcare professionals, especially the clinical pharmacist, must know the most potent and clinically significant interactions and adverse events and use them to identify and minimize drug-related problems, as demonstrated in studies [26].

CONCLUSION

This study identified that drugs used empirically for COVID-19, when administered together with drugs that act on the CNS, can cause several drug interactions, requiring monitoring of use to promote greater safety in the treatment.

Thus, the presence of the clinical pharmacist working in the hospital environment is of great importance, as he is a professional capable of assisting in the tracking of adverse drug events and optimizing the patient's pharmacotherapy, through pharmacotherapeutic review and monitoring. These pharmaceutical interventions prove to be valid as they enable the reduction of errors related to medications, resulting in treatment success and therapeutic efficacy.

In addition, the need to continue studies in this area is evident, aiming to increase the knowledge of the health team about drug-drug interactions and enable the implementation of strategies and protocols that help the medical team to identify potential interactions and adopt preventive measures. and monitoring of patients at risk of developing drug interactions.

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