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Potential risk of investigated drugs for the treatment of COVID-19: drugs interactions

Risco potencial dos medicamentos investigados para o tratamento da COVID-19: interações medicamentosas

Riesgo potencial de los medicamentos investigados para el tratamiento de COVID-19: interacciones medicamentosas

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ABSTRACT

Introduction: The coronavirus causes infections in lower respiratory tract and with preceding cases by the Coronavirus of the Severe Acute Respiratory Syndrome (SARS-CoV) and by the virus of the Middle East Respiratory Syndrome (MERS-CoV). It was aimed to investigate the potential interactions, of severe and moderate degrees, of the drugs tested in the treatment of COVID-19 with other drugs and with diseases. **Outline**: Characterizes itself as a documentary research that use the data base Drugs® for obtaining the cross information of the data banks with another drugs, according to articles of periodicals indexed in the great searchers PubMed, Science Direct and BVS. For the determination of the drug interaction, there were used only the data which had at least “good documentation” and only the interactions “expressly contraindicated”, “major” and “moderate”, the mild interactions were omitted. **Results**: The hydroxychloroquine and the chloroquine are associated with many drug interactions and with drugs, along to the azithromycin, which also has a high degree of risks. However, the nitazoxanide, the ivermectin and the oseltamivir are in the opposite direction, with small drug interactions and low risks to the treatment safety. The monoclonal antibodies and the antiretrovirals have balanced risk-benefit relation. **Implications**: Most of the currently investigated drugs in the treatment of COVID-19 show several drug interactions and interactions with pre-existing diseases.

DESCRIPTORS

Coronavirus; Virus Replication; Drug Interactions.

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INTRODUCTION

In December 2019, in Wuhan, China, it have been started the reports of a severe idiopathic pneumonia.[1] After, laboratory researches detected the virus, denominated coronovirus.[2] The coronavirus causes infections in the lower respiratory tract and with previous cases of infection by the Coronavirus of the Severe Acute Respiratory Syndrome (SARS-CoV) and by the virus of the Middle East Respiratory Syndrome (MERS-CoV).[3] The cases in Wuhan increased exponentially and the virus disseminated for several countries. On January 30, the World Health Organization (WHO)[4] declared this scenario as public health emergency. The virus was detected as a new beta coronavirus of enveloped RNA, denominated SARS-CoV-2 (COVID-19).[5]

The genesis of this virus is unknown, however there are reports that correlate the initial cases to a seafood market, in Wuhan, at where wild animals are commercialized.[6] Due to disease progress in several countries all around the world, on March 11, 2020, the WHO[4] declared the novel coronavirus as a pandemic, once the confirmed cases rose abruptly in divers countries, with serious cases leading to deaths.[7] Infection's pathophysiology is similar to the SARS-CoV, where it happens a series of inflammatory responses with risk group persons getting worse, such as cardiac patients, diabetics, the elderly.[8] The main symptoms are: fever, dry cough and dyspnea. Generally, the incubation period ranges 2 to 14 days after the infection.[9]

As to the therapeutics, there emerged studies pointing out to a possible effectiveness of chloroquine and/or hydroxychloroquine and its association with azithromycin on COVID-19 treatment. However, the massive development of studies about prophylactic and healing therapies for the exhibited a possible absence of safety and efficiency of that therapy, accompanied of eventual risk of mortality in risk group, severe and mild cases. Other alternatives with more secure potential were tested and employed on COVID-19 treatment, are examples the antifungals ivermectin and nitazoxanide, antibodies tocilizumab and sarilumab, antivirals oseltamivir, ritonavir/lopinavir and azithromycin, beyond of aspirin for thromboembolic events and prednisolone for respiratory complications, both from A2 treatment stage.

To elucidate the questions about the risks and benefits of these medicines, the aim of this study was to investigate the potential interactions, severe and moderate degrees, of the tested medicines on COVID-19 treatments with another medicines and diseases.

METHOD

Characterizes itself as a documentary research, of quantitative approach, retrospective and analytical-discursive. The research was grounded in the use of data taken from the electronic platform Drugs® (https://www.drugs.com/drug_interactions.html), which is a database that provides information about medicaments, mostly about drugs interactions, to obtain crossed information about the use of medicaments compared to other medicaments and several diseases, that is, interactions drug-drug and drug-disease.

For a better foundation of this study, articles of periodicals indexed in the great searchers PubMed, Science Direct and BVS were used, to confront the data for a correct grounding and to have knowledge of the existent risks in the use of each medicament investigated in the COVID-19 concomitant to other in-use medicaments and preexist diseases in the in-question patient. After obtaining the answers resulting from drug-drug and drug-disease interactions, it is possible to validate the results obtained in this study, since Drugs® is an international scientific platform used by health professionals in the clinic for safe management of patient therapy.

For the determination of the drug interaction, there were used only the data available in the Drugs® of at least "good documentation" and only the interactions "expressly contraindicated", "major" and "moderate", the mild interactions were omitted. The "drugs" used in this study all are commercially available medicaments. There were used, as including criterium, the medicaments investigated *in vitro* way, *in vivo* or clinically for the COVID-19, whether for prophylaxis or treatment. There were used, as excluding criteria, the medicaments used in the disease A2 treatment stage for treating complications.

RESULTS

Table 1 exhibits the main potential interactions of the hydroxychloroquine, of moderate and severe degrees, with another medicaments and diseases, showing 1 (one) severe drug interaction with leflunomide, may leading to the increasing of infections risk; and 5 (five) moderate drug interactions with the leflunomide, calcium 600 D, beyond of the risk of QT prolongation in the use of amitriptyline, albuterol, and tramadol. In relation to the hydroxychloroquine interactions with diseases, the severe risk in cases of oculotoxicity and porphyria highlight, as well as moderate risks in cases of arrhythmia, myelosuppression, ototoxicity, convulsions, hepatotoxicity, psoriasis, diabetes, heart diseases and renal insufficiency, totalizing 2 (two) severe risk restrictions and 8 (eight) of moderate risk ones.

Table 1 – Potential interactions of hydroxychloroquine with medicaments and diseases.

HYDROXYCHLOROQUINE	
Medicaments	**Responses**
Amitriptyline ++; Albuterol ++; Azithromycin +++; Tramadol ++	QT Prolongation
Calcium 600 D ++	Reduces the BA of the chloroquine
Duloxetine ++	Augments the BA of the duloxetine
Leflunomide +++	Can enhance the risk of infections
Diseases	**Responses**
Oculotoxicity +++	Oculotoxicity to the retina
Porphyria +++	Exacerbation of porphyria
Arrhythmia ++	QT Prolongation
Myelosuppression ++	Depression of blood cells
Ototoxicity ++	Can lead to hearing problems
Convulsions ++	Possible convulsions in patients
Hepatotoxicity ++	Can lead to liver failure
Psoriasis ++	Can lead to a crisis
Diabetes ++	Severe hypoglycemia
Hearth diseases ++	Cardiomyopathy in high doses
Renal insufficiency ++	Can cause kidney failure

Legend: +++: severe; ++: moderate; BA: bioavailability.

Table 2 demonstrates the main drug interactions of the chloroquine, of moderate and severe degrees, with another medicaments and disease, demonstrating 10 (ten) medicament/medicament interactions with mefloquine, pregabalin, duloxetine, albuterol, primaquine, budesonide/formoterol, hydroxyzine, ciprofloxacin and, specially, the azithromycin and the hydroxychloroquine, because they are usual in concomitant use in the COVID-19 and exhibit potential risks of QT prolongation. In relation to the chloroquine interactions with disease, there were evidenced 8 (eight) potential risk interactions with the use, oculotoxicity and the porphyria of severe

degree; and arrhythmias, myelosuppression, ototoxicity, convulsions, hepatotoxicity, and moderate degree psoriasis, highlighting for the arrhythmias which can lead for QT prolongation, totalizing 17 severe and moderate interactions resultant of the chloroquine use.

Table 2 – Potential interactions of chloroquine with medicaments and disease.

CHLOROQUINE	
Medicaments	**Responses**
Hydroxyzine ++; Azithromycin ++; Ciprofloxacin ++; Hydroxychloroquine ++; Primaquine ++; Albuterol ++; Budesonide/Formoterol ++	QT Prolongation
Duloxetine ++	Enzyme Inhibition of the duloxetine
Pregabalin ++	Decreases the antiepileptic effectiveness
Mefloquine ++	Can cause convulsion and arrhythmias
Diseases	**Responses**
Oculotoxicity +++	Oculotoxicity to the retina
Porphyria +++	Can exacerbate the porphyria
Arrhythmia ++	QT Prolongation
Myelosuppression ++	Depression of erythrocytes and leukocytes
Ototoxicity ++	Can lead to hearing problems
Convulsions ++	Possible convulsions
Hepatotoxicity ++	Can lead to liver failure
Psoriasis ++	Can lead to a crisis

Legend: +++: severe; ++: moderate.

The Table 3 exhibits the potential risk of azithromycin in drug/drug and drug/disease interactions, of severe and moderate degrees, showing 4 (four) interactions with another medicaments, of moderate degree, with warfarin, floticasone/salmeterol, albuterol, and budesonide/formoterol, which can lead to QT prolongation. In relation to the drug/disease interactions, the azithromycin shows 2 (two) severe potential risks in cases of colitis and QT prolongation and 2 (two) moderate potential risks in cases of liver disease and severe myasthenia, totalizing 8 (eight) severe and moderate interactions deriving out of the use of azithromycin.

Table 3 – Potential interactions of the azithromycin with drugs and diseases.

AZITHROMYCIN	
Medicaments	**Responses**
Floticasone/Salmeterol; Albuterol ++; Budesonide/Formoterol ++; Hydroxychloroquine +++; Chloroquine ++	QT Prolongation
Warfarin ++	Augmentation of the effects (HPTB)
Diseases	**Responses**
Colitis +++	Can alter the normal flora of the colon
QT Prolongation +++	Cardiac Events
Liver Disease ++	Aggravation of liver problems
Severe Myasthenia ++	Exacerbation of myasthenia-related symptoms

Legend: +++: severe; ++: moderate; HPTB: hypoprothrombinemia.

The Table 4 exhibits the potential risk of the nitazoxanide, in severe and moderate degrees, of interactions with drugs and diseases, showing 1 (one) drug/drug moderate interaction with the valproic acid 3 (three) moderate interactions drug/diseases with diabetes, kidney and liver diseases, totalizing potential risk of 4 (four) moderate interactions and no severe.

Table 4 – Potential interactions of the nitazoxanide with drugs and diseases.

NITAZOXANIDE	
Medicaments	**Responses**
Valproic Acid ++	The nitazoxanide can increase the bioavailability of the valproic acid
Diseases	**Responses**
Diabetes ++	Hyperglycemia
Kidney/Liver Disease ++	Can cause kidney and/or liver failure Biliary obstruction

Legend: ++: moderate.

The Table 5 shows the potential risks of using lopinavir/ritonavir in relation to the severe and moderate degrees interactions with another medicaments and diseases, showing 1 (one) possible severe interaction with the phenytoin and 6 (six) possible interactions of moderate degree with atazanavir, valproic acid, emtricitabine/tenofovir, dexamethasone and, especially, ciprofloxacin and azithromycin, as they have the potential of QT prolongation. As to the potential interactions of the lopinavir/ritonavir with diseases, the hemophilia and the hepatotoxicity show severe response potential to the use, while the hyperglycemia, hyperlipidemia and the heart block represent moderate potential risk to the use.

Table 5 – Potential interactions of antiviral drugs with another drugs and diseases.

LOPINAVIR / RITONAVIR	
Medicaments	**Responses**
Atazanavir ++	Enzyme inhibition of the Atazanavir
Azithromycin ++; Ciprofloxacin ++	QT Prolongation
Dexamethasone ++	Enzyme inhibition of the Dexamethasone
Phenytoin +++	Attenuates the effect Lopinavir/Ritonavir
Emtricitabine/Tenofovir ++	Nephrotoxicity
Valproic Acid ++	Enzyme Induction of the Valproate
Diseases	**Responses**
Hemophilia +++	Potential risk of bleeding
Hepatotoxicity +++	Hepatic problems (icterus, AST, ALT)
Hyperglycemia ++	Insulin resistance, GI
Hyperlipidemia ++	TC, TG and CAD augmentation and atherosclerosis
Heart Block ++	PR interval prolongation and atrioventricular block

Legend: AST: aspartate aminotransferase; ALT: alanine aminotransferase; TC: total cholesterol; TG: triglycerides; CAD: coronary artery disease; +++: severe; ++: moderate; GI: glucose intolerance.

The Table 6 demonstrates the potential interactions of severe and moderate degrees exerted by using monoclonal antibodies in view of another drugs and disease, showing the leflunomide with severe potential of generating effects to the use and the atorvastatin, methotrexate, amlodipine, probiotics, and the hydroxychloroquine showing moderate potential of effects to the use of monoclonal antibodies. In relation to the potential interactions with the diseases, the immunizations and the infections show a severe degree as response to the use and the tuberculosis, demyelinating disorders, gastrointestinal perforation, liver dysfunction, and the renal insufficiency with moderate potential risk to the use.

Table 6 – Potential interactions of the monoclonal antibodies with drugs and diseases.

TOCILIZUMAB	
Medicaments	**Responses**
Leflunomide +++	Intensifies the risk of grievous infections
Atorvastatin ++	Enzyme induction of the atorvastatin
Methotrexate ++	Potential risk of hepatotoxicity
Amlodipine ++	Enzyme induction of the amlodipine
Hydroxychloroquine +++	Peripheral neuropathy
Probiotics ++	Augments the risk of infections
Diseases	**Responses**
Immunizations +++	Vaccine ineffectiveness
Infections ++	Severe infections potentiating
Tuberculosis ++	Worsening of tuberculosis
Demyelinating disorders ++	Worsening of disorders
Gastrointestinal perforation ++	Risk of gastrointestinal perforation
Liver dysfunction ++	Unknown safety and efficacy
Renal insufficiency ++	Unknown safety and efficacy

Legend: +++: severe; ++: moderate.

The Table 7 points out interactions, of severe and moderate degrees, exerted by the concomitant use of the investigated medicaments in the COVID-19 treatment, showing potential severe interactions between the concomitant use of the hydroxychloroquine versus azithromycin versus tocilizumab versus lopinavir/ritonavir, the hydroxychloroquine also exerts the potential risk with the chloroquine, but in a moderate way. Besides that, the chloroquine still presents a moderate risk in the concomitant use with lopinavir/ritonavir, tocilizumab, and azithromycin, as well as lopinavir/ritonavir versus ivermectin versus azithromycin. Nitazoxanide and oseltamivir do not have considerable potential risk of interaction among the medicaments investigated in the treatment of COVID-19.

Table 7 – Potential interactions among the drugs investigated on COVID-19 treatment.

DRUGS USED IN COVID-19	HZQ	CQ	NTZ	L/R	OTM	IVC	TCZ	AZT
Hydroxychloroquine	=	++	–	+++	–	–	+++	+++
Chloroquine	++	=	–	++	–	–	++	++
Nitazoxanide	–	–	=	–	–	–	–	–
Lopinavir / ritonavir	+++	++	–	=	–	++	–	++
Oseltamivir	–	–	–	–	=	–	–	–
Ivermectin	–	–	–	++	–	=	–	–
Tocilizumab	+++	++	–	–	–	–	=	–
Azithromycin	+++	++	–	++	–	–	–	=

Legend: HZQ: hydroxychloroquine; CQ: chloroquine; NZX: nitazoxanide; L/R: lopinavir/ritonavir; OTM: oseltamivir; IVC: ivermectin; T/S: tocilizumab/sarilumab; AZT: azithromycin; +++: severe; ++: moderate; –: without interaction; =: the same drug.

DISCUSSION

The Hydroxychloroquine (HZQ) has been widely studied on COVID-19 treatment, since the precociuous[10] one as the late one,[11] with the improvement by its use, however, the doubt defines the current scenario, once a lot of another studies refute the efficiency of those,[12] as well show the absence of safety of the HZQ[8] through the increasing of the risk of death by means of, especially,

cardiovascular complications[2] as arrhythmias and QT prolongation.[13]

A systematic review showed the increasing of the risk of cardiovascular events when used the HZQ[12] in relation to the control, just like is showed above that in cases of concomitant use the amitriptyline,[14] albuterol and tramadol[15] augment the existent risk of the use of HZQ. Besides that, it is important to highlight the risk of emergence of infections,[16] once the virus, by its own, makes the patient immunosuppressed. This study also shows that the spontaneous improvement of COVID-19 affected patients naturally occurs on 80% of the cases.[17]

In one study,[18] it had been observed the need of careful handling before the moderate risk in a possible utilization of the HZQ, like in patients with liver problems, diabetic ones, kidney problems and, above all, in hearth problems which are well evidenced in clinical studies.

Besides that, many drugs potentiate chloroquine cardiac effects, especially, the HZQ, by synergism, and the Azithromycin (AZT),[13] both usually considered to be as front line in COVID-19 treatment, however, with the risk of QT prolongation and ventricular arrhythmias,[19] worrying events, where cardiac patients incorporate the risk group of the COVID-19, as the studies show.[20-21]

In vitro[22] and *in vivo*[2] studies show the decreasing in the mortality of patients affected with the COVID-19 by means of the use of the chloroquine, exhibiting a recovery in patients treated with the medicament, showing to have therapeutic potential through the decreasing of the viral replication. The virus binds to an isoform of the angiotensin-converting enzyme,[23] located in the pulmonary alveoli and responsible for developing cardiac events, which explains the respiratory and cardiac problems of the COVID-19 of those patients.[24]

Many studies points out the AZT as one of the drugs with higher therapeutic potential in the treatment of the COVID-19, by this reason it is employed in the first line of treatment in medical clinic.[25-26,13] However, its elevated cardiotoxic potential worries, once its possesses risk of QT prolongation and ventricular arrhythmias, just like Table 3 shows and corroborated by the studies.[27-28]

The interaction of the AZT with the HZQ and the chloroquine raises the warning sign of that therapy,[29] once the COVID-19, by its own, is a problem for cardiovascular patients, like hypertensive patients, patients with non-rhythmic heartbeats, patients with cardiac insufficiency, patients with a history of Acute Myocardial Infarction (AMI).[30] However, the AZT with 4- aminoquinolines derived ones potentiates this imminent risk, how the study also shows.[31]

Its utilization must also be cautious in thrombotic-events patients, once the AZT potentiates the hypoprothrombinemia effects,[32] besides of it becoming necessary to track the hepatic markers to ensure that patients with liver deficiency don not get their functional state aggravated by using the macrolide, just as it is shown.[33]

Studies of the nitazoxanide (NZX) in the treatment of COVID-19 are more incipient regarding to the HZQ, to the chloroquine and to the AZT, however, there also have evidences about its antiviral therapeutic potential,[34] in addition to being widely used in medical clinic. Although the above-mentioned medicaments there have more studies in the treatment of COVID-19, the NZX highlights because of its low potential of promoting adverse effects relevant in the therapeutics.[35]

The Table 4 presents the moderate potential risk of the NZX in promoting enzyme inhibition in the hepatic metabolism of the valproic acid in concomitant use.[36] Besides that, it can promote hyperglycemia in diabetic patients, due the fact of it possessing saccharose in the composition, according to the Brazilian Pharmacopedia,[37] as well as renal and hepatic dysfunctions in patients with commitments in these functions.[38-39] The Ivermectin, another antiparasitic, mentioned in Table 7, which was investigated in this research, do not demonstrates

interactions with significant potential risk,[40] showing up safety, but still with incipient studies in the viral treatment.

The antiretrovirals Lopinavir/Ritonavir are a widely used association in the treatment and prevention of HIV by means of the inhibition of the viral multiplication through protease inhibition.[41] This association in question has its greatest potential risk in association with phenytoin, once it suffers enzyme induction and, because of this, it can have its antiretroviral effects attenuated.[42] Besides that, the LPN/RTN plays moderate potential risk against another four important drugs in the treatment of COVID-19, among they, the AZT, showing risk of QT prolongation and ventricular arrhythmias, quite evident in patients with the disease.[19]

The patients affected with cardiac problems and diabetics, by their own, are two risk groups in the COVID-19. However, the use of the LPN/RTN still can lead to insulin resistance and to glucose tolerance in hyperglycemic[43] patients and, also, blockade of the essential cardiac functions and QT prolongation,[18] this way, presumably potentiating the hyperglycemic and cardiac effects in patients with these conditions.

The Tocilizumab (TCZ) is a monoclonal antibody tested in the treatment of COVID-19.[44-45] The TCZ has a potential risk of serious infections when used with leflunomide, because of its immunosuppressant effect.[46] Besides that, the concomitant use of the TCZ with HZQ has the high risk of generating diabetic neuropathy.[47] TCZ use in patients utilizing amlodipine, probiotics and atorvastatin must be tracked for the possible risk adverse effects of these medicaments.

It is possible noticing that HZQ use in association with the AZT, TCZ, LPV/RTN, moderate risk with the chloroquine and the use with the NTZ, Oseltamivir (OTM) and IVC, demonstrating that the most recommended therapies in antiCOVID-19 treatments have a high risk, especially the cardiovascular ones,[19,31,48-50] as showed in the Table 1. The AZT in associated use with other medicaments in COVID-19 treatment, has a high risk when utilized with 4- aminoquinolines derived ones, in addition to the antiretroviral ones.[19] Its use becomes safer when used with the NTZ, OTM, IVC, TCL,[49] however its use is commonly used with either the HZQ or the CQ,[25] a not recommended therapy[51] and unsafe.[13]

Although the HZQ, CQ and AZT are the most investigated drugs in COVID-19 treatment, the NZX, the IVC and the OTM are the drugs which have the lowest potential risks of interactions with drugs and disease, showing they have the greatest safety in the use of COVID-19.[52-53] Once there are several studies hypothesizing therapeutical effects and therapeutic ineffectiveness of all candidates to the COVID-19 “cure”, there is no definite scientific confirmation about none, by this reason, considering the risks each one presents, added to the risks generated by the virus itself, therapies that provide less risk to the infected patients are assumed to be the best choice.

Therefore, it is necessary to carry out more robust and solid studies to finally clarify these open questions and fill all the gaps and biases that still exist about all the drugs investigated here. Once all studies face limitations, this, in turn, had as main limitation to deal only with potential cases, without analyzing all the need practice to avoid these interactions to happen.

CONCLUSION

At the end of this study, it was possible noticing that most of the medicaments currently investigated in COVID-19 treatment shows several drug interactions and interactions with preexistent diseases, revealing high and moderate risks in their use, even in an isolated manner and, largely, strengthened when associated with certain medicaments and diseases.

It is worth mentioning that some interactions must be relativized, because it is necessary to evaluate the relevance of each interaction in view of the patient’s clinical status, hence, patient’s

therapeutic monitoring must be carried out by the involved multidisciplinary team and must be observed whether these interactions alter the state of the patient or if the generated effects as from that interaction are harming the therapy in question, in this case, the therapeutical continuity is dictated by the risk-benefit analysis.

Moreover, it can be inferred that the most worldwide used medicaments are the ones which have more interactions and therapeutical risks in their use, once the most related complication in COVID-19, the cardiovascular problems, also are caused by the hydroxychloroquine use or chloroquine use and strengthened by the azithromycin, even without clear scientific proof of their benefits.

RESUMO

Introdução: O coronavírus provoca infecções nas vias aéreas inferiores e com casos de infecções precedentes pelo coronavírus da Síndrome Respiratória Aguda e da Síndrome Respiratória do Oriente Médio. Objetivou-se investigar as interações potenciais, de graus grave e moderado, dos fármacos testados no tratamento da COVID-19 com outros fármacos e doenças. **Delineamento**: Caracteriza-se como uma pesquisa documental que utiliza a base de dados Drugs® para a obtenção das informações cruzadas dos bancos de dados com outros fármacos, conforme artigos de periódicos indexados nos grandes buscadores PubMed, Science Direct e BVS. Para a determinação de Interação medicamentosa, foram utilizados apenas os dados que dispunham de no mínimo "boa documentação" e apenas as interações "expressamente contraindicadas", "maiores" e "moderadas", as interações leves foram omitidas. **Resultados**: A hidroxicloroquina e a cloroquina estão associadas a muitas interações medicamentosas e com doenças, juntamente à azitromicina, que também possui um grau alto de riscos. Contudo, a nitazoxanida, ivermectina, oseltamivir estão do outro lado da margem, com pequenas interações e riscos à segurança do tratamento. Os anticorpos monoclonais e os antirretrovirais possuem risco benefício equilibrado. **Implicações**: A maioria dos medicamentos atualmente investigados no tratamento da COVID-19 apresentam diversas interações medicamentosas e interações com doenças preexistentes.

DESCRITORES

Coronavirus; Replicação Viral; Interações Medicamentosas.

RESUMEN

Introducción: El coronavirus provoca infecciones en las vías respiratorias inferiores y con casos de infecciones previas por el coronavirus del Síndrome Respiratorio Agudo y Síndrome Respiratorio de Oriente Medio. El objetivo fue investigar las posibles interacciones, de grados severos y moderados, de los fármacos probados en el tratamiento del COVID-19 con otros fármacos y enfermedades. **Delineación**: Se caracteriza por ser una investigación documental que utiliza la base de datos Drugs® para obtener información cruzada de las bases de datos con otros fármacos, según artículos de revistas indexadas en los principales buscadores PubMed, Science Direct y BVS. Para la determinación de interacción farmacológica, solo se utilizaron datos que tuvieran al menos "buena documentación" y solo las interacciones "expresamente contraindicadas", "mayor" y "moderada", se omitieron las interacciones leves. **Resultados**: La hidroxicloroquina y la cloroquina se asocian con muchas interacciones entre medicamentos y enfermedades, junto con la azitromicina, que también tiene un alto grado de riesgo. Sin embargo, la nitazoxanida, la ivermectina y el oseltamivir están del otro lado del margen, con interacciones menores y riesgos para la seguridad del tratamiento. Los anticuerpos monoclonales y antirretrovirales tienen un beneficio-riesgo equilibrado. **Implicaciones**: La mayoría de los fármacos que se investigan actualmente en el tratamiento de COVID-19 tienen varias interacciones farmacológicas e interacciones con enfermedades preexistentes.

DESCRIPTORES

Coronavirus; Replicación Viral; Interacciones Farmacológicas.

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There are no conflicts of interest to declare.