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A review of cardiovascular involvements associated with medications used to treat COVID-19 infection

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SOUHRN

Koronavirové onemocnění 2019 (COVID-19) se rychle rozšířilo po celém světě a vyvolalo globální krizi zdravotnických systémů. Toto onemocnění dnes představuje jednu z nejzávažnějších pandemií v historii lidstva; přitom postihuje řadu orgánů včetně celého kardiovaskulárního systému. U pacientů s onemocněním COVID-19 bylo popsáno poškození myokardu, myokarditida, akutní infarkt myokardu, dysrytmie a srdeční selhání. V současné době není k dispozici žádné specifické antivirotikum pro léčbu onemocnění COVID-19; zatím se používají některá léčiva jako interferon, remdesivir, ribavirin, favipiravir a tocilizumab. Tyto látky používané při léčbě onemocnění COVID-19 mohou mít nežádoucí účinky na kardiovaskulární systém, případně mohou interagovat s jinými farmaky určenými k léčbě kardiovaskulárních onemocnění. Nejzávažnějšími nežádoucími účinky těchto farmak jsou prodloužení intervalu QT a torsade de pointes (TdP), které mohou vést k náhlému úmrtí. V tomto článku popisujeme nežádoucí účinky různých farmak na kardiovaskulární systém i možné interakce mezi látkami používanými při léčbě onemocnění COVID-19 a farmaky uplatňujícími se v kardiologii.

Keywords:
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ABSTRACT

Coronavirus disease 2019 (COVID-19) pandemic has spread rapidly across the world and is introduced as a global health crisis. COVID-19 is one of the threatening pandemics in history involving many organs, including the cardiovascular system. The cardiovascular involvements, such as myocardial injury, myocarditis, acute myocardial infarction, dysrhythmias, and heart failure, have been reported in the COVID-19 patients. Currently, there is no specific antiviral treatment for COVID-19; though, some therapies such as interferon, remdesivir, ribavirin, favipiravir, and tocilizumab are being used. The medications used to treat COVID-19 may have cardiovascular adverse events or interact with some cardiovascular drugs. The most concerning conditions caused by these medications are QTc prolongation and torsades de pointes (TdP), which might cause abrupt death. Here, we describe cardiac adverse effects and potential interactions of COVID-19 medications with cardiovascular agents.

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Introduction

Coronavirus disease 2019 (COVID-19) pandemic is known to have originated from Wuhan, China, in late 2019.[1–3] This viral infection was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By August 31, 2020 there have been 21 026 758 confirmed cases of COVID-19, including 755 786 deaths, reported to the World Health Organization (WHO).[4] The pandemic is spreading quickly in the world. COVID-19 is one of the most threatening pandemics in history involving several organs, including the cardiovascular system, which leads to more severe disease, intensive care unit (ICU) admission, and mortality.[5]

Cardiovascular involvement may occur through various mechanisms and include respiratory failure, hypoxemia due to progressive cardiac load, direct myocarditis or cardiomyopathy, indirect effects of the systemic inflammatory response, and drug interaction.[6]

The important concerns about the association between cardiac complications during COVID-19 therapy are hospital severe cases with increased death. Furthermore, these patients are usually taking cardiac medications for their underlying cardiovascular disorder.

A medication used to treat COVID-19 may interact with some cardiovascular drugs such as antihypertensive or antiarrhythmic agents, anticoagulant or antiplatelet drugs, and statins.[7] Although, these adverse reactions occur frequently with long-term use. The most concerning and significant conditions caused by these medications are QTc prolongation and torsades de pointes (TdP), which might lead to sudden death.[8] Here, we review cardiac adverse effects and potential interactions of COVID-19 medications with cardiovascular agents.

Medication interactions

Hydroxychloroquine and chloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) were one of the first drugs proposed as a treatment for COVID-19, which belongs to the antimalarial class.[9] HCQ/CQ has been widely administered to patients with COVID-19. This agent functions through changes in endosomal/organelle pH. However, it is potentially harmful to the heart and causes cardiotoxicity through different mechanisms such as impairing electrolyte balances, especially potassium channel blocking, prolongation of the QT interval, or drug-drug interactions.[10,11]

Risk factors for the development of HCQ-induced cardiotoxicity include long-term use (greater than 3 months), higher doses, underlying heart disease, and renal failure.[12] It may interact with antiarrhythmic medications such as beta-blockers (metoprolol, carvedilol, propranolol, and labetalol), and digoxin.[13] In the case of co-administration, it suggests reducing beta-blockers and digoxin doses, while monitoring electrocardiogram (ECG).

They can lead to direct myocardial toxicity, cause restrictive or dilated cardiomyopathy, worsen the pre-existing cardiomyopathy, and cause dysrhythmias through inducing hypokalemia.[14,15]

They might influence the cardiac system and result in different arrhythmias such as QTc prolongation, ST and T wave depression, U-wave, bundle branch block, atrioventricular (AV) block, TdP, sick sinus syndrome, and sino-atrial node arrest.[16] Atrial fibrillation and ventricular tachycardia are the most prevalent ones in the settings of HCQ/CQ use, alone or in combination with a macrolide.[12]

Less common cardiac complications are left ventricular hypertrophy or hypokinesis, heart failure, valvular involvement, and pulmonary arterial hypertension. On rare occasions, irreversible cardiac damage such as death, need for a pacemaker, and heart transplantation has been reported.[17] CQ/HCQ-related cardiac toxicity can be sub-grouped into these categories:[16] (1) sudden deaths; (2) cardiac arrests; (3) ventricular arrhythmias (i.e. TdP and syncope); (4) conduction disorders (with or without QTc prolongation); (5) isolated prolonged QTc.

TdP, an uncommon polymorphic ventricular tachycardia may be induced by CQ/HCQ.[8] It is important to note these arrhythmias develop more commonly in individuals with preexisting QT prolongation, higher doses, and also in combination therapy with QT-prolonging agents such as macrolides.[18]

The dose of HCQ required to cause cardiotoxicity in each person may differ markedly from each other. Also, the cardiotoxicity of HCQ is more likely to appear with cumulative doses. Therefore, it is recommended to optimize the HCQ dosage based on pharmacokinetic (PK) characteristics in patients.[19]

It is important to note, the complete atrioventricular block is more common with CQ; whereas, left ventricular hypokinesis is much more related to HCQ.[20] Furthermore, injection reactions with CQ are much more common than HCQ. Generally, HCQ/CQ is banned in individuals with congenital long QT syndrome or those with a prior history of TdP.[21] However, one study demonstrated that HCQ/CQ may decrease the risk of cardiovascular complications in rheumatologic patients, possibly due to atherosclerosis reduction.[22]

Protease inhibitors

Protease inhibitors including lopinavir/ritonavir (LPV/r) and atazanavir (ATV) were another group of medications proposed as a treatment during the COVID-19 pandemic.[23] LPV/r was more commonly used compared with ATV. However, it had multiple adverse effects including cardiac complications and drug-drug interactions.

Arrhythmias reported to be triggered by LPV/r include various cardiac conduction abnormalities such as bradycardia-tachycardia syndrome, QTc prolongation, AV blocks,and TdP.[24] Also, LPV/r tends to raise serum cholesterol levels and predisposes to atherosclerosis.[25] Furthermore, LPV/r may cause serious drug interactions with anticoagulants, antiplatelet, antiarrhythmic, and statins.[26] Interactions with apixaban, edoxaban, rivaroxaban, and warfarin among commonly used anticoagulants seem to be more significant. In these situations, apixaban should be taken with a half dose and should not be received more than 2.5 mg twice daily. Monitoring international normalized ratio (INR) in warfarin co-administration is necessary.[27] Rivaroxaban and edoxaban are contraindicated in the case of LPV/r use.[28] Other medications may

interact with LPV/r are antiplatelet agents such as clopidogrel and ticagrelor, while prasugrel can be an appropriate alternative.[26,29]

Also, interaction with statins such as atorvastatin, rosuvastatin, lovastatin, and simvastatin has been reported.[30] In this situation, gradually increasing the dose of rosuvastatin and atorvastatin is reasonable, whereas lovastatin and simvastatin should not be co-administered. Switching to pitavastatin or pravastatin can be another option while LPV/r is necessary.[31] Another consideration is the potential drug reactions between LPV/r and antiarrhythmic agents such as digoxin and ranolazine.[32] In these situations, the digoxin dose must be decreased and its level should be monitored, whereas ranolazine should not be co-administered. The ATV has been utilized in some patients, due to the vast range of adverse reactions induced by LPV/r and because of ATV has less interaction with other co-administered medications compared with LPV/r.

Studies have shown that ATV similar to LPV/r can affect QTc interval.[33] However, the ATV is the only protease inhibitor that does not cause dyslipidemia. Some dysrhythmias reported in the settings of ATV include AV block, bradycardia, and TdP.[34] Dysrhythmias can lead to sudden cardiac death, particularly in patients with underlying heart disease.

Ribavirin

Ribavirin inhibits viral protein synthesis as a result of the inhibition of RNA and DNA replication.[35] It was used in severe cases of COVID-19. No significant cardiovascular adverse events have been reported for this agent, except severe hemolytic anemia which may lead to high cardiac output heart failure.[36] It can interact with anticoagulants such as warfarin through an unknown mechanism of action.[37]

Favipiravir

It has recently tested the efficacy of favipiravir for treating COVID-19 and found clear treatment benefit. Favipiravir exerts an antiviral effect through the inhibition of RNA-dependent RNA polymerases; however, it can lead to QT interval prolongation.[38] Also, it can interfere with anticoagulant, antiarrhythmic, and statin therapy.[39]

Remdesivir

Remdesivir is a nucleotide analog inhibitor of RNA-dependent RNA polymerases from SARS-CoV-2 with high potency. Some adverse effects of remdesivir such as hypotension, various dysrhythmias, atrial fibrillation, deep-vein thrombosis, septic shock, and cardiac arrest have been reported.[40,41] However, cardiovascular drug interactions have not yet been reported.[42]

Interferon

Interferons proved effective in the current pandemic. However, interferon may induce myocardial toxicity through worsening the pre-existing cardiomyopathy, hypotension, ischemic attacks, cardiogenic shock, and pericardial effusion.[43] Its interaction with warfarin has been reported, so monitoring of INR and reduction in warfarin dose may be needed.[37]

Glucocorticoids

Glucocorticoids such as dexamethasone and methylprednisolone are very effective in reversing adverse pulmonary immunologic reactions of COVID-19, which lead to a reduction in COVID-19 mortality.[44] However, adverse events of glucocorticoids such as fluid overload, hypertension, and electrolyte disarrangements have been reported and their interaction with anticoagulant agents such as warfarin is a point of care.[45]

Monoclonal antibodies

Monoclonal antibodies such as tocilizumab and sarilumab are interleukin-6 (IL-6) inhibitor used for the treatment of rheumatologic disorders, which are used for suppressing cytokine storm in COVID-19 infection.[46] Fortunately, these agents are not arrhythmogenic and have no risk of precipitating factors leading to heart failure decompensation. Although, shortening of the QT interval hypercholesterolemia , hypertension, and drug-drug interactions have been reported.[47] The most significant interactions are with antiarrhythmics such as amiodarone, anticoagulants (i.e. apixaban, rivaroxaban, and warfarin), antiplatelets such as ticagrelor and clopidogrel, statins (i.e. simvastatin, atorvastatin, and lovastatin), and beta-blockers (i.e. metoprolol, carvedilol, propranolol, and labetalol).[48] Also, no dose adjustment is needed and merely monitoring of INR and ECG seems to be sufficient.

Other medications suggested theoretically or proved to be beneficial in the COVID-19 treatment

Anakinra and pirfenidone

No cardiac adverse events have yet been reported.

Bevacizumab

It may cause cardiomyopathy or exacerbates the pre-existing one. Also, severe hypertension and thromboembolic accidents have been reported.[49]

Eculizumab

Tachyarrhythmias, hypertension or hypotension, and peripheral edema have been reported along with the use of eculizumab.[50]

Fingolimod

Hypertension, AV blocks, bradyarrhythmias, and QTc prolongation have been reported. Fingolimod is contraindicated after myocardial infarction, angina pectoris, and cerebrovascular events.[51] Furthermore, it may interact with medications such as beta- blockers, and calcium channel blockers, and class Ia and class III antiarrhythmic drugs.[52]

Colchicine

Despite, no cardiac side effects have been seen but colchicine may interact with non-DHP calcium channel blockers such as verapamil and diltiazem, and statins (i.e. simvastatin, atorvastatin, fluvastatin, lovastatin, and pravastatin).[53]

Convalescent plasma

There is no evidence of direct cardiovascular adverse events, except potential transfusion-related complications such as circulatory overload.[54]

Antimicrobials

Antimicrobials carry the risk of following cardiotoxicities:[55–59] (1) piperacillin-tazobactam has been shown to induce TdP; (2) fluoroquinolones such as levofloxacin may potentially prolong the QT interval and caution should be taken with co-administering them with class I and class III antiarrhythmic drugs and in electrolyte imbalances; (3) vancomycin has not been reported to induce any cardiac adverse events, except the vascular collapse; (4) azithromycin also has been implicated in QTc prolongation and proarrhythmic events, particularly with CQ/HCQ. It can interact with anticoagulants, antiarrhythmics, other QT prolonging agents, and statins. Previously, it had been shown that a combination of CQ/HCQ with a macrolide might pose challenges for cardiovascular safety.[60] In the current pandemic COVID-19, because of the antimicrobial, immunomodulatory and anti-inflammatory effects of azithromycin, and their synergistic effects in eliminating virus replication, combination therapy with CQ/HCQ has been quite prevalent.[61] Some authorities believe that the combined treatment not only has not proven efficacy but also poses harm and toxicity for high-risk patients. Factors that predispose to these adverse events include coronary artery disease, heart failure, previous cardiac arrhythmias, and chronic obstructive pulmonary disease. Therefore, in high-risk populations, we should take precautions in administering the mentioned combination therapy. The combination of azithromycin and HCQ can cause arrhythmias due to metabolic changes including hypomagnesemia, hypocalcemia, and hypokalemia, or acute renal failure.[62,63] In other words, this combination may have additive effects on QT prolongation.[64] It has been shown that minocycline can be a good alternative to azithromycin. It is believed that minocycline may prevent QT prolongation.

Conclusion

We should pay attention to the point that patients in the convalescent phase of COVID-19 might be so debilitated and reluctant to take their routine cardiac medication such as beta-blockers and antiplatelet, which may pose a significant risk of their underlying cardiac condition decompensation, or induce newly occurring coronary artery disease. It is important to note, in terms of cardiotoxicity with patients receiving antiviral agents, we cannot attribute the events to drugs adverse effects or interactions, since COVID-19-induced cardiomyopathy or myocarditis might be responsible for the condition.

Conflicts of interest

All authors declare no conflict of interest.

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Ethical statement

Authors state that the research was conducted according to ethical standards.

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