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Original article

Practical prescribing with COVID-19 medications and psychotropics: a guide to pharmacokinetic interactions

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SUMMARY

Background
The risks of pharmacological interactions increase significantly with the number of drugs a patient is prescribed. Patients with coronavirus (COVID-19) infection and mental disorders often receive several medications, and they may interact.

Methods
We examined the existing literature with the goal to: 1) review the bases of pharmacokinetic interactions between psychotropics and medications that are prescribed to treat COVID-19 infection and its complications; 2) examine the implications for clinical practice.

Results
Pharmacokinetic interactions are possible and may cause adverse effects or decrease the efficacy of one or more of the medications a patient is taking.

Conclusions
A thorough evaluation of the pharmacokinetic interactions is necessary when COVID-19 medications are prescribed to patients with mental disorders that are treated with psychotropic medications. The risk of pharmacokinetic and pharmacodynamic interactions should inform treatment choice and may require dosing adjustments.

Key words: Coronavirus, COVID, interactions, psychotropics, psychiatric, pharmacological, medications, cythocrome, inhibitor, inducer

Introduction

Although COVID-19 pandemic seems to have subsided in some Countries, the illness is continuing its spread across the world. As of June 7, there were about 7 million confirmed cases in 188 countries [1]. To date, the time and way in which the pandemic will end is impossible to predict and this is made more complex because of issues such as easy transmissibility, relatively long time (2-10 days in most cases) before the symptoms appear, and inter-individual differences in terms of symptoms that are developed, going from no to deadly symptoms [2].

Patients with mental illness are at risk of being infected at least as much as everyone else. The infection, or the worry about the risks and consequences of getting infected, may worsen existing mental disorders or contribute to the onset of new diseases.

The risks of pharmacological interactions increase significantly with the number of drugs that a patient receives [3]. Patients with coronavirus (SARS-CoV2 or COVID-19) and mental disorders often receive more than one medication and therefore the risk of interactions is relatively high. Indeed, COVID-19 causes delirium in a significant proportion of acutely infected

patients and increases the risk for anxiety, depression, or post-traumatic stress disorder. Given that patients with mental disorders may be infected with COVID-19 and patients with COVID-19 may develop a mental disorder, the number of people that are prescribed a psychotropics and COVID-19 has increased. We hereby review the bases of drug-drug interactions and examine the possible interactions between psychotropics and drugs that are most frequently prescribed as a treatment for COVID-19.

Disclaimer

Information presented in this paper is intended only as a partial summary of data available in the public domain. No clinical consultation or advice is implied or given for any specific patient. Clinicians must exercise their own judgement and evaluate the risks and benefits of single and combined medications, which includes but is not limited to the evaluation of pharmacokinetic and pharmacodynamic interactions between two or more medications. The clinician is the only and ultimate responsible for treatment choice and administration, after consulting all the available sources, not limited to this manuscript. The prescriber shall hold the Authors, Editors, Reviewers and Publisher harmless against any consequences arising from the use or application in clinical practice of any information reported in this paper.

Drug-drug interactions

A drug-drug interaction occurs when one drug alters the levels or the pharmacological effects of a second drug. Clinically significant interactions may substantially alter, boost or lessen the activity of one of the drugs, or both. Pharmacological interactions are usually described as either pharmacodynamics or pharmacokinetics. Pharmacodynamic interactions take place at the organ or at the receptor level. Pharmacokinetic interactions, on the other hand, occur when a drug interferes with the absorption, distribution and transport, metabolism or elimination of a second drug. For example, both benzodiazepines and alcohol act on the GABA A receptor, increasing the conductance to chlorine, decreasing neuronal activity and determining a series of clinical effects, including sedation, reduction of anxiety, muscle relaxation and amnesia. If benzodiazepines and alcohol are taken together, a pharmacodynamic interaction occurs, resulting in an excess of the effect that these substances individually would produce, or excessive sedation, motor defects and respiratory depression, which can be fatal [4].

Pharmacokinetic interactions, on the other hand, occur when a drug interferes with the absorption, distribution and transport, metabolism or elimination of a second drug [4]. Alterations in absorption occur in the gastrointestinal tract, for example if a drug causes a change in gastric pH, a mechanical blockage of the mechanisms responsible for absorption or a modification in the bowel flora. The alterations in distribution and transport occur instead when, for example, two drugs bind to the same transport proteins. In this case, the drug that has the greatest tendency to bind will increase the concentration of the free fraction of the second drug, which is pharmacologically active. An example of a therapeutic substance very sensitive to protein-related displacement is warfarin. Metabolic interactions occur instead when a drug reduces or accelerates the enzymatic metabolism by one second. This is the most frequent pharmacokinetic interaction. Finally, an interaction in the elimination happen when a drug reduces the excretion of a second medicament, for instance when the lithium and some diuretics are administered concurrently [5-9].

Biotransformation

The biotransformation of a medication usually goes through two phases: phase 1 and phase 2 [10]. Phase 1 occurs mainly in microsomes and concerns functionalization through oxidative reactions such as O-dealkylation (for example codeine), N-dealkylation (for instance imipramine), aliphatic hydroxylation (which concerns midazolam), aromatic hydroxylation (amphetamines), n-oxidation (for example acetaminophen), S-oxidation (which concerns chlorpromazine), or deamination (for example diazepam) [11]. This process makes the substances more manageable for phase 2. phase 2 concerns conjugation, via endogenous cofactors (such as glucoronic acid, sulphate, glycine) that act on the functional groups present in the substance or introduced during phase 1. The enzymes involved are a group of transferases that transfer the cofactor to the substrate [11]. The result is an amplification in polarity and the potential for urinary and biliary excretion. While most conjugations hesitate in a biological inactivation or detoxification, in some cases they can give a bioactivation. Most of the enzymes involved in phase 2 are allocated in the cytosol, with the exception of uridine-diphosphoglucoronic-transferase (UDPTG), which are microsomal. Phase 2 reactions are typically faster than phase 1 reactions which act as a stopper in the metabolization path. Some medications are metabolized through phase 1, followed by phase 2, others are metabolized only through phase 1 or only through phase 2 [10].

Phase 1

The most important enzyme system that presides phase 1 is the cytochrome P 450; in nature there are more than 200 P450 enzymes, of which at least 40 have been categorized in humans. However, six isoenzymes are involved in least 90% of the entire enzyme activity of cytochrome P450: 1A2, 2C9, 2D6, 2C19, 2E1, and 3A4; all

these enzymes are located in the smooth endoplasmic reticulum of the hepatocytes and in the luminal epithelium of the small intestine. There is a genetic variability (polymorphism) of CYP P450 and marked differences may exist between individuals of different races. Each person has two copies of each gene (allele); variations of the common alleles are generally described as "genetic polymorphisms". Individuals with a genetic polymorphism characterized by a malfunctioning allele or the absence of an allele are defined as "poor metabolisers", instead subjects who have several copies of the common alleles are described as "ultra-rapid metabolisers" [12]. A common drug interaction mechanisms occurs through the inhibition or induction of the CYP P450 system. The affinity of a drug for CYP P450 is called inhibitory potential or Ki; Ki values lower than 2 micromoles are typically indicators of a powerful inhibition. When two drugs are administered simultaneously, the drug with higher affinity (low Ki) competitively inhibits the binding of the drug with less affinity (high Ki) [12-13]. Some drugs bind to an enzyme and inhibit it, without however needing that enzyme for their own metabolism, while other medications are both substrates and enzyme inhibitors. Inhibition of the P450 system is immediate and when treatment with the inhibitor is stopped the system quickly returns to normal functionality. Certain drugs and substances, such as cigarette smoke, induce the synthesis of P450 proteins and increase the of sites available for biotransformation, with consequent loss of efficacy for medications that are deactivated by that system or risk of drug toxicity with potentially harmful metabolites [10-13].

Cytochrome P450 2D6

Cytochrome P450 2D6 (CYP-450-D6) is located in the endoplasmic reticulum and intervenes in the oxidative metabolism of a series of exogenous or endogenous compounds through hydroxylation, dealkylation or demethylation reactions. For example, 2D6 is responsible for activities such as the hydroxylation of tricyclic antidepressant drugs, the N-demethylation of fluoxetine, and the N-dealkylation of metoclopramide, the hydroxylation of progesterone [10-13]. The cytochrome 2D6 gene is located on chromosome 22, with more than 30 polymorphisms that have been reported. Recent studies have indicated the presence of a high percentage (up to 50%) of poor metabolizers (or zero metabolizers) in people of Asian, African, or African-American origin and of the Pacific islands. In the Caucasian race, this percentage is "only" 26%. The metabolism of drugs oxidized through 2 D6 is obviously altered in these patients [14-17].

For instance, risperidone is normally converted from 2D6 into its 9-hydroxy metabolite. If a person is a poor (or, even more so, null) metabolizer, the medication is obliged to "choose" as the main metabolizer the 3 A4 isoenzyme, for which it has less affinity and the patient will have higher blood levels of risperidone, and more side effects [18].

Genotiipic analyzes of cytochrome P450 are possible, especially in cases where a drug with a narrow therapeutic index is prescribed.

Cytochrome P450 3A4

Cytochrome P450 3A4 (CYP-3A4) is certainly the most represented in humans and presides more than 50% of all drug-oxidation reactions in the liver8. Like 2D6, 3A4 intervenes in the phase 1 oxidative metabolism of exogenous and endogenous compounds, for example steroid hormones, cholesterol or lipids [9-13]. Although 3A4 polymorphisms have been described, the clinical significance is still at the center of controversy and debate. What is certain is that 3A4 is part of the 3A sub-family (the other variations are 3A5 and 3A7) and that the enzymatic activity of 3A changes according to the percentage in which the three variations are expressed [19].

CYP-3A4 inhibitors

There are many 3A4 inhibitors, including grapefruit juice, the antifungals itraconazole and ketoconazole, diltiazem, the macrolide antibiotics erythromycin, troleandomycin and clarithromycin, norfluoxetine, nefazodone, ciprofluoxacin, la norfluoxacin [9-13,19]. The latter drug, together with ketoconazole, is an extremely powerful inhibitor, with ki values in the order of nanomoles instead of micromoles. Cases of death have been reported due to the association of drugs such as pimozide with drugs such as antifungals, probably caused by excessive blood concentration of pimozide, leading to longer duration of cardiac repolarization (Qtc) and a torsades de pointes up to fibrillation ventricular [9-13, 19].

For this reason, the association of pimozide with antifungals, macrolides, protease inhibitors, etc. is contraindicated today. Hence, when a 3A4 inhibitor is administered together with a 4A4 substrate, appropriate adjustments of the dose are necessary [20]. Thus is particularly important for medications with low therapeutic index, such as calcium channel blockers, for a risk of hypotension and arrhythmias, or inhibitors of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase for a risk of rhabdomyolysism, or triazolobenzodiazepines such as alprazolam, midazolam, estazolam and triazolam, or hypnotics such as zolpidem and zaleplon, for the risk of excessive sedation [9-13, 19-20]. It is also important to remember that 3A4 inhibitors can worsen the side effects of oral contraceptives, given the interaction with the metabolism of estradiol [19-20].

CYP-450-3A4 inducers

One of the most known is carbamazepine, which is both

a substrate and an inducer of 3A4. In addition, carbamazepine induces conjugation, phase 2 enzymes. Oxcarbamazepine also induces 3A4 and is therefore able to alter the concentrations of other medications that metabolized via this cytochrome, such as oral contraceptives. Inducers include drugs such as nevirapine and efavirenz, rifampin and rifabutin antitubercular, troglitazone, prednisone and dexamethasone, modafinil, hypericum. Ritonavir is a potent 3A4 inhibitor but can become an inducer after a few weeks of therapy [9-13, 19-20].

Cytochrome P-450 1 A2

Unlike the other cytochromes, CYP P450 1A 2 (CYP-1A2) is localized exclusively in the liver. CYP-1A2 presides the oxidative reactions (primarily hydroxylation and demethylation) of medications such as methylxanthines (e.g. caffeine and theophylline) and endogenous compounds such as 17 Beta estradiol and uroporphyrinogen. When a medication is metabolized from both 2D6 and 1A2, 2D6 (high affinity, low capacity) acts when the drug is at low concentration, while 1A2 starts working when the concentration of the drug in question increases and 2D6 is saturated [9-13, 19-20].

CYP-1A2 inhibitors

One of the most known 1A2 inhibitors is fluvoxamine. Potent inhibitors are also drugs such as fluoroquinolone antibiotics (e.g., ciprofluoxacin, enoxacin, lonefloxacin), theophylline, mexiletine and propafenone. Other inhibitors include grapefruit juice and the antiandrogen metabolite flutamide. Important 1A2 substrates include clozapine, cyclobenzaprine, flutamide, flovatriptan, melatonin, mirtazapine and caffeine (which like melatonin and theophylline depends on 1A2 for more than 90% of its oxidative metabolism). Examples of interaction at the level of 1A2 are those of fluvoxamine with haloperidol, imipramine and clozapine, whose blood concentrations can increase up to over 600% when they are co-administered with fluvoxamine. In many cases (for example in that of clozapine and fluvoxamine) the interactions extend other 1A2, since fluvoxamine is also a potent inhibitor of 2C9 and 2C19 and, albeit less powerful, of 3A4 and 2D6, and is therefore, for example, for example in the case of interaction with clozapine, able to influence all the main pathways of metabolization of the drug CYP-1A2 inducer. Tobacco smoke is one of the most known inducers of 1A2. More specifically, smoking increases the metabolism of olanzapine (metabolized by 1A2 and, to a lesser extent, by 2D6) by about 40% and also can increase the clearance of clozapine by even greater percentages8. It is therefore appropriate to appropriately adjust the dosage of these medications in patients who smoke. Instead, people who quit smoking, the prescribed dose should usually be reduced after a few weeks, since the induction process (and return to normal once the inducer is suspended) is not immediate [9-13, 19-20]. Of interest, there is a polymorphic variation of 1A2 which is not affected by smoking [21].

Cytochrome P-450 2C9

Cytochrome P-450 2C9 (CYP-2C9) metabolizes a limited number of drugs, some of which, such as non-steroidal anti-inflammatory drugs and oral hypoglycaemic agents, are however in common use. The main activities of 2C9, like that of the other P450 enzymes, includes hydroxylation, demethylation and dealkylation of exogenous and endogenous compounds [9-13, 19-20]. Also in this case genetic differences exist and therefore again we speak of scarce and rapid metabolizers [13-19]. Cytochrome 2C9 inhibitors include drugs such as ritonavir, sulfafenazole, fluvoxamine, fluconazole, modafinil, desethylamiodarone (metabolite of amiodarone), zafirlukast and, perhaps to a lesser extent, fluoxetine, paroxetine and sertraline. The S isomer of warfarin is an example of a drug with low therapeutic index that is metabolized by 2C9, while its R isomer is instead metabolised mainly by CYP 1A2. Rifampin is instead an example of an inducer of 2C9.

Cytochrome P-450 2C19

Cytochrome P-450 2C1 (CYP-2C19) is similar to CYP 2C9 but not identical. Similarly to the other CYP 450 isoenzymes, CYP-2C19 presides over hydroxylation, demethylation and dealkylation of exogenous and endogenous compounds. Also in this case there are polymorphysymes, poor metabolisers and rapid metabolisers. An example of a powerful CP-2C19 inhibitor is fluvoxamine; other inhibitors are ticlopidine, omeprazole, fluoxetine, ritonavir, oral contraceptives and perhaps paroxetine. An example of substrate is diazepam [9-13, 22].

Other cytochromes

Several other isoenzymes of cytochrome P450 have been described. Examples include 2E1 (which is induced by alcohol and inhibited by disulfiram), 2A6, 2B6, and 2C8 [9-13, 19-22].

P-Glycoprotein

P-Glycoprotein (PGY-1) is a glycosylated and phosphorylated membrane protein consisting of two monomers of approximately 600 amino acids each [23-24].

Each monomer has a hydrophobic and a hydrophilic polarity. It is present in various cellular districts (proximal renal tubules, biliary canaliculi, small and large intestine, pancreatic ducts, adrenal, blood brain barrier astrocytes) where it binds a large variety of mostly hydrophobic substrates by removing them from the cell (the letter “P” stands for “Permeability”), using energy from the hydrolysis of ATP (adenosine triphosphate) [23-24]. Its discovery and isolation in the 70s are linked to

the study of the phenomenon of drug resistance which prevented the success of chemotherapy, for which cells seemed to become "impervious" to antiblastic drugs 9. Its function would be to expel substances in the excretory pathways and to protect some districts (brain) from an accumulation of toxic substances [23-27].

In the intestinal lumen, p-glycoprotein has the task of rejecting a fraction of the substrates initially absorbed: the meaning would be to modulate the passage of xenobiotics in the blood, allowing in particular to Cyp3A4, also very present in enterocytes, to cope to an excess of substrate for a first biotransformation. The possible negative implication of this regulatory mechanism obviously lies in the possibility of reducing the availability of drugs [23-27]. For example, quinidine increases blood levels of dioxin through the inhibition of glycoprotein in the intestine and kidney. Other examples of glycoprotein inhibitors that can increase the dioxin concentration (mainly by initiating renal p-glycoprotein) are nifedipine, nitrendipine, felodipine, atorvastatin, verapamil, clarithromycin, propafenone, cyclosporine, amiodarone and itraconazole. On the contrary, rifampin decreases the concentration of dioxin through the induction of intestinal PGY-1. In this case, a portion of the dioxin initially absorbed is rejected in the intestinal tract. Another example of a PGY-1 inducer is hypericum, which can increase the activity of glycoprotein 1.5 times, reducing the blood levels of some drugs such as digoxin [23-28]. Since hypericum is also an inducer of CYP-3A4, drugs that are substrates of both CYP-3A4 and PGY-1 undergo a double effect (double induction). Examples of double inhibitors instead include ketoconazole and erythromycin. In the brain, PGY-1 excretes some of the drugs that manage to pass the blood brain barrier. Most psychotropic drugs are not PGY-1 substrates and can therefore reach adequate concentrations. For example, first generation antihistamines are not PG-Y1 substrates and therefore give sedation; on the contrary, second generation antihistamines are actively expelled from the PG-Y1. Another medication that is actively expelled by PGY-1 is loperamide, an antidiarrheal. When loperamide is administered with quinidine (a PG-Y1 inhibitor), there is a risk of respiratory depression and death, because of an increase in its concentration in the brain. As in the case of cytochrome P450, there are also genetic differences for PGY1 which are evident in the ability to absorb / reject certain specific drugs in different individuals [24-29].

Interactions between COVID medications and psychotropics

A number of patients affected by coronavirus develop or were already affected by a mental illness. Combination treatment of COVID medications and psychotropics may cause adverse events or loss of efficacy. For instance, a side effect that is relatively common for COVID-19 medications is prolongation of the EKG repolarization interval QT, which is commonly observed also for many psychotropics. Hence, COVID-19 and psychotropics may synergically increase QT. Baseline and post administration ECG is necessary in these situations [30].

Hydroxychloroquine

Hydroxychloroquine has been associated to adverse effects such as neutropenia, seizures, myocardial toxicity, and arrhythmia. Cardiovascular side-effects may include cardiac failure, cardiomyopathy, and several arrhythmias and electrocardiographic changes such as T wave inversion, flattened T wave, widened QRS complex, bundle branch or atrioventricular block, longer QT interval,, ventricular tachycardia, torsade's de pointes, and ventricular fibrillation [30-31]. Therefore, hydroxychloroquine should not be prescribed on top of psychotropic medications that have similar risks, for instance clozapine.

Ritonavir/lopinavir

Ritonavir/lopinavir are contraindicated if patient is on drugs that are metabolized for by the cytochrome CYP-450-3A4 because ritonavir is a potent CYP-3A4 inhibitor. Therefore, any psychotropic which is metabolized mainly through CYP3A4 (buspirone, clonazepam, carbamazepine, lurasidone, quetiapine, mirtazapine, pimozide, trazodone and many others) should be stopped or dose adjusted. For instance, when quetiapine is prescribed in combination with ritonavir/lopinavir, the FDA recommends reducing the dosage of quetiapine to 1/6th and to monitor for related adverse effects [34]. Of interest, ritonavir/lopinavir are themselves substrates of CYP3A. Hence, it should not be prescribed in combination with medications that able to inhibit (e.g., fluvoxamine) or induce (e.g., carbamazepine, topiramate) CYP3A4. Finally, ritonavir/lopinavir, may reduces serum levels of medications such as Valproate or Lamotrigine, because of their tendency to induce their glucuronidation (phase 2) in the liver. Hence, dose adjustments are needed [32-33, 35-36].

Azithromycin

Azithromycin, can increase QTc duration and the coadministration of psychotropics with the same ability should be avoided or prescribed with caution. Also, azithromycin can cause acute increases in liver aminotransferase /transaminases so should be used cautiously in patient on drugs that are potentially hepatotoxic, such as valproate or carbamazepine. When the co-administration is necessary, regular monitoring of liver function tests is in order [37-38].

Remdesivir

Remdesivir, has been authorized only recently by the United States Food and Drug Administration for emergency use in patients with severe complications from COVID-19 and only limited data is available about its potential interactions with psychotropics. This medication is a prodrug of a nucleotide analog, which inhibits viral RNA-dependant RNA polymerase [39]. Remdesivir has shown efficacy against Ebola and acute respiratory syndrome induced by coronavirus. To our knowledge, there is no published report of prolonged QTc, torsades de pointes, or arrhythmias due to remdesivir. Nonetheless, it is known that remdesivir may elevate liver enzymes, which suggest caution when it is co-administered with medications such as valproate or carbamazepine [38].
Remdesivir is a substrate for CYP450-2C8, 2D6, and 3A4, along with p-glycoprotein and organic anion transporting polypeptides 1B1 (OATP1B1) [40]. When coadministered with medications able to induce CYP-3A4, such as carbamazepine, phenobarbital, phenytoin, and St John's wort, there is a potential decrease in remdesivir concentration. For instance, antipsychotics like thioridazine (in Countries where thioridazine is still available, since many Countries have withdrawn this medication from the marked because of the risk of QTc prolongation and arrythmia) require close monitoring or dose adjustment. Thioridazine is metabolized by CYP2D6 and to a lesser extent by CYP3A4 [38,40]. Therefore, although remdesivir inhibits CYP3A4 it is unlikely to have a significant effect on thioridazine. However, thioridazine is a moderate inducer of CYP3A4 and may reduce remdesivir concentrations. Remdesivir is also an inhibitor of CYP3A4 and should be used with caution in patients treated with medications primarily metabolized by this isoenzyme [38,40-41].

Tocilizumab

Tocilizumab is a recombinant monoclonal antibody, anti-human IL-6 receptor that is primarily used as a treatment for rheumatoid arthritis but is also being studied as a medication for respiratory failure in patients affected by COVID-19 [42-43]. *In vitro* studies showed the ability of tocilizumab to induce multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In vivo studies with simvastatin, which is metabolized by CYP3A4, showed a 57% decrease in exposure, one week after a single dose of tocilizumab. In vivo studies with omeprazole, which is metabolized by CYP2C19 and CYP3A, showed a 28% decrease in exposure, again one week after a single dose of tocilizumab. The ability of tocilizumab to induce CYP enzymes may be clinically relevant particularly for CYP450 substrates with narrow therapeutic index [44].

More and updated information

A comprehensive and frequently updated list of interactions with COVID medications is provided in open access by the University of Liverpool Drug Interaction Group [45-46].

Conclusions

The combination of COVID and psychotropic drugs is often necessary and, in most cases, the benefits outweigh the risks. Pharmacodynamic and pharmacokinetic interactions are possible and must be taken into consideration to avoid adverse effects or reduced efficacy. This is made more important because of genetic polymorphisms that are responsible for large inter-individual differences in the ability to metabolize medications, with poor and ultra-rapid metabolizers that may achieve very high or very low blood concentration of a given compound. In most cases, COVID medications can be safely prescribed in combination with psychotropic drugs. However, a thorough evaluation of the pharmacodynamic and the pharmacokinetic interactions can inform the most appropriate choice of drugs and doses and help reducing the risks of inefficacy or adverse events.

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