Review Article

Common anti-COVID-19 drugs and their anticipated interaction with anesthetic agents

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Abstract

The corona virus disease 2019 (COVID-19) pandemic has till date (26/7/20) affected 1crore 62 lac 73 thousand 638 people globally with almost 6.5 lakh mortalities. COVID-19 has invaded the operation theatre and intensive care unit (ICU) in a short span of 6 months. It appears inevitable that all of us, as anesthesiologists, have to treat COVID-positive patients, either in the ICU or the operation theatre. Many asymptomatic, presumably noninfected people including frontline health care workers are also consuming potential anticorona viral drugs (such as hydroxychloroquine) prophylactically and may present for surgery. Detailed knowledge of which anesthetic and perioperative care drugs can interact with anti-COVID drugs would be very valuable for pre, intra-, and postoperative management of such patients and COVID-19 positive patients requiring intubation, mechanical ventilation, and ICU-sedation. Powered with this knowledge, anesthesiologists and intensivists can minimize the adverse effects of drug interactions. An extensive literature search using different search engines including Cochrane, Embase, Google Scholar, Scopus, and PubMed for all indexed review articles, original articles, case reports, and referenced webpages was performed to extract the most current and relevant literature on drug-drug interactions for clinicians.

Keywords: Anesthetic drugs, azithromycin, COVID-19, dexamethasone, favipiravir, hydroxychloroquine, ivermectin, nitazoxanide, remdesivir, ritonavir, tocilizumab

Introduction

The ongoing corona virus disease-2019 (COVID-19) pandemic has struck mankind like a thunderbolt: the roars of thunder coming much later than the lightning. The COVID-19 pandemic has till date (26/7/20) affected 16,273,638 people globally with 6,49,549 mortalities.[1] The Indian picture (26/7/20) stands at 1.39 million confirmed cases with 32,063 deceased.[2] After 2 months and four lockdowns in an effort to contain the disease, the government declared that we "have to learn to live with COVID-19" and ushered in the unlock-phases.[3] It is anticipated that the number of severe acute respiratory syndrome corona virus-2 (SARS-CoV-2)-positive patients will only increase. SARS-CoV-2 is a positive-sense single-stranded RNA-virus infecting human beings to produce a spectrum of clinical features ranging from asymptomatic infection to fatal acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC).[4] Whether COVID-19 prophylaxis is achievable or is a mirage remains to be seen, but the battery of candidate drugs being empirically tested is ever-increasing. These drugs have important anesthetic implications that cannot be overlooked in the pre, intra-, and postoperative periods and also during intubation, mechanical ventilation, and ICU sedation of suspected/COVID-positive patients.

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Hydroxychloroquine[5,6] (HCQ) in particular has emerged as the central drug undergoing several clinical trials for pre-and postexposure prophylaxis and treatment of COVID-19 infection alone or in combination with several other drugs such as bromhexine, nitazoxanide (NTZ), remdesivir, and azythromycin. Ritonavir (Indian Council of Medical Research (ICMR) authorized for restricted public health emergency use for COVID-19) and methylprednisolone are also in common use in India.[7] Glenmark has received the Drugs Controller General of India (DCGI) approval for conducting a phase-3 human trial for combination therapy with favipiravir and umifenovir, which are the two antiviral drugs with different mechanisms of action.[8] Interactions of these drugs with anesthetic agents have been reviewed at length here.

Methods

For easy comprehension, we have classified the anti-COVID drugs into three broad categories [Table 1]. The first category comprises drugs which have obtained an emergency use authorization (EUA) by the Food and Drug Administration (FDA) for COVID-19 (HCQ and Remdesivir).[9] The second category comprises nitazoxanide (NTZ), azithromycin, favipiravir, and toclizumab due to a large number of ongoing global clinical trials with promising results.[8,10,11] Ritonavir, dexamethasone, and ivermectin being in common use in India are also included. A third category comprising vitamin/mineral (Vitamin-C, Vitamin-D, Vitamin-E, zinc, and magnesium) supplements and Indian/Chinese herbal extracts (turmeric, lemon juice, giloy, basil, cinnamon, black-pepper, ginger, garlic, huangqui, forsythia, and fangfeng) being used as immunity-boosters is beyond the scope of this manuscript.

An extensive literature search using different search engines including Cochrane, Embase, Google Scholar, Scopus, and PubMed for all indexed review articles, original articles, case reports, and referenced webpages was carried out using keywords coronavirus, COVID-19, treatment, prophylaxis. Out of the 18,020 articles obtained, which described 47 drugs, 9 drugs were selected for review. The next search included keywords: drug interaction, hydroxychloroquine, remdesivir, ritonavir, nitazoxanide, azithromycin, favipiravir dexamethasone, ivermectin, and tocilizumab with over 21000 results. Hence, clinically important drug-interactions of each of these drugs (except remdesivir) with anesthetic agents were extracted from www.drugs.com (data sources include IBM Watson Micromedex, Cerner Multum™ and Wolters Kluwer™). Reference crawling was utilized to extract the most current and relevant literature on drug-drug interactions. We would like to caution the readers that these drug-interactions are extrapolations of the side effects and drug-interactions reported in current literature for non-COVID-19 patients based on the authors' perception. However, no such data for real-time interaction has been reported in COVID-19 patients and real-time study and data is yet to emerge.

Discussion

Although no drug has yet obtained FDA approval, a battery of drugs is currently undergoing human clinical trials as "anti-COVID-19 therapeutic agents."

Table 1: Classification of anti-corona virus-19 drugs

Category	Basis of categorization		Name of Drug
Category 1	FDA approved		HCQ Remdesivir
Category 2	Off-label use	Ongoing global clinical trials	NTZ Azithromycin Favipiravir Tocilizumab
		Widespread use in India	Ritonavir Dexamethasone Ivermectin
Category 3	Vitamin/mineral supplements Alternate medicine	Vitamin Mineral Supplements	Vitamin-C Vitamin-D Vitamin-E Zinc Magnesium
		Indian (Traditional)	Giloy Turmeric Basil Cinnamon Black pepper Ginger Garlic
		Chinese (Traditional)	Huangqui Forsythia Fangfeng

Several antiviral drugs (baloxavir, favipiravir, HIV-protease inhibitors, oseltamivir, remdesivir, and umifenovir) and supporting drugs (anakinra, ascorbic acid, azithromycin, baricitinib, colchicines, corticosteroids including depot methylprednisolone, COVID-19 convalescent plasma, ruxolitinib, sarilumab, siltuximab, sirolimus, and tocilizumab are currently undergoing human clinical trials. Inhaled drugs like epoprostenol and nitric oxide are also under investigation.[12,13]

Many other drugs such as HCQ, chloroquine phosphate, ACE-inhibitors, angiotensin-II receptor blockers, low-molecular-weight heparin, unfractionated heparin, famotidine, statins, intravenous immunoglobulins ivermectin, nebulized drugs, niclosamide, nitazoxanide, nonsteroidal anti-inflammatory drugs (NSAIDS), and tissue plasminogen activators including alteplase also look promising.[12,13] Bacillus Calmette–Guérin (BCG) and measles, mumps, and rubella (MMR) vaccination are also being used for COVID-prophylaxis.[14,15]

The mechanisms of action, doses, and side effects of commonly used anti-COVID drugs have been tabulated for easy reference [Table 2].

We summarize below the drug interactions of the first two categories of anti-COVID drugs with anesthetic and perioperative care drugs [Table 3].

Category I (Drugs with FDA emergency use authorization)

Hydroxychloroquine (HCQ)

Empirical/off label use of HCQ for COVID-19, spread like wildfire after it was endorsed by the Indian Council of Medical Research (ICMR).[16] It is yet to obtain FDA approval although it has obtained emergency use authorization.[9] An effective antimalarial, HCQ also finds widespread use in several autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus Hashimoto thyroiditis) due to its immunosuppressant action.[17] Diabetes mellitus, breast, prostatic, and pancreatic cancer are other clinical indications for HCQ.[17,18]

The terminal half-life of HCQ is 32–50 days.[19] Hence, there is no need for advice of discontinuation of HCQ 5–7 days before surgery in the preanesthesia check-up (PAC) clinic. Any patient who has consumed HCQ up to 6 half-lives before surgery may potentially suffer pre-, intra-, and postoperative drug-drug interactions with HCQ.

QT-interval prolongation is a major side-effect of HCQ. As tachycardia can shorten QT-interval by reducing ventricular repolarization time, heart rate-corrected QT-interval (QTc), obtained by Bazett's formula (QT upon the square root of R-R interval) has better clinical relevance.[20,21] QTc exceeding 450 ms in males and 470 ms in females qualifies as prolonged QTc.[21] Although a positive correlation exists between the risk of cardiac events and the magnitude of QT-prolongation, no cutoff QTc value has been identified for ventricular arrhythmias. Torsades-de-Pointes is known to occur at QTc ≥500 ms .[21,22]

Several antiarrhythmics (Class-I; Class-III), antipsychotics, antidepressants, antibiotics (macrolide; quinolone), antifungals, baricinitib, ondansetron, and some opioids (methadone; tramadol) also prolong QTc [Table 3].[23,24] Their additive/synergistic effect with HCQ may prove disastrous. Propofol has also been incriminated in causing QT-prolongation.[25,26] Anesthetic-induction, maintenance of anesthesia, or procedural sedation with propofol should be avoided in patients on HCQ, ritonavir, or azithromycin anti-COVID-19 therapy. Drugs inhibiting cytochrome P450 3A4 (CYP3A4), cytochrome P450 1A2 (CYP1A2), and cytochrome P450 2D6 (CYP2D6) prolong the action of drugs undergoing hepatic metabolism by this route and indirectly cause QT-prolongation if administered with drugs directly causing QT-prolongation.

Intestine-luminal endothelial cells and the blood-brain barrier contain the P-glycoprotein efflux transport pump, which is inhibited by HCQ.[27] Elevation of cyclosporine and digoxin levels are the resultant drug interactions with HCQ, both digoxin and cyclosporine being substrates of P-glycoprotein system.[28]

Immunocompromised patients (cancer-chemotherapy, steroids for autoimmune disorders/organ transplant recipients) are at risk being more vulnerable firstly, contracting COVID-19 and secondly, a more severe course. Hence, before partaking HCQ-prophylaxis they need to know that HCQ is also an immunosuppressant and interacts with cyclosporine.

HCQ should not be co-administered with drugs (Aspirin, NSAIDS, quinolones, sulphonamides, methylene-blue) that cause hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals.[29] Caution needs to be exercised for procedures that require methylene-blue instillation like cuff-inflation of laser-resistant tubes.

Immunologically-mediated adverse reactions

HCQ has been implicated in severe cutaneous adverse reactions, (Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS).Manifestations include

Table 2: Mechanism of action, dose and side effects of anti-corona virus-19 drugs

Drug	Mechanism of action	Dose	Side effects
Hydroxychloroquine (HCQ)[5,6,15-23]	Increased endosomal pH, →prevention of virus/cell fusion. Interferes with glycosylation of cellular receptors of SARS-CoV. Control the cytokine storm that occurs in critically ill late phase SARS-CoV-2	Pre-exposure prophylaxis 400 mg twice daily on day-1 400 mg once/week for 8 weeks Or 200 mg daily for 2 months Post-exposure prophylaxis: 400 mg twice daily on day-1 200 mg twice daily for days 2-5 Treatment: 200 mg 3 times/day for 10 days	QT-prolongation Nausea; Vomiting Abdominal pain Diarrhea Rashes Retinopathy Hemolysis in G6PD deficient patients Neuromyotoxicity
Nitazoxanide (NTZ)[43-46]	Phosphorylation of protein kinase activated by double-stranded RNA → ↑phosphorylated factor 2-alpha (antiviral); Interference with drug detoxification, unfolded protein response, autophagy; anti-cytokine activity; c-Myc inhibition.	Nitazoxanide 500 mg oral every 6 hours for 6 days	Pain abdomen Nausea; Diarrhea Flatulence Thirst; Headache Dizziness; Tremor Fever; Pruritis Eye discoloration Amenorrhea
Remdesivir[34-41]	Nucleoside analog that inhibits the action of RNA-dependent RNA polymerase. Dodges proofreading by viral exoribonuclease→premature halt of viral RNA transcription	200 mg intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir for total of 10 days	Nausea, vomiting, Rectal hemorrhage Hepatotoxicity
Azithromycin[56-59]	Enhancement of anti-SARS-CoV-2 activity of HCQ	500 mg on day 1, followed by 250 mg once daily on day 2-5)	QT prolongation Palpitations
Ritonavir[53-55]	Inhibition of papain-like protease and 3C-like protease	Day1: 400 mg orally twice daily; Days 2-14 100 mg twice daily	Vomiting, Diarrhea, Rash, Palpitations; Hepatorenal injury
Favipiravir[60-64]	Inhibition of the RNA-dependent RNA polymerase	Day 1: 1600 mg twice daily; Days 2-14: 600 mg twice daily	Diarrhea Hepatorenal injury
Ivermectin[65-67]	Nuclear transport inhibitory activity	12mg once daily for 7 days	Vomiting, Diarrhea, Arthralgia, Fever, Pruritis Rash, Conjunctivitis
Tocilizumab[70]	Interleukin-6 receptor inhibitory monoclonal antibody	8 mg/kg once daily	Neutropenia, Thrombocytopenia, Hyperlipidemia, Transaminitis

G6PD-Glucose six phosphate dehydrogenase; HCQ-Hydroxychloroquine; RNA-Ribonucleic acid; SARS-CoV-2- Severe acute respiratory syndrome corona virus-two

new-onset fever, exanthema, or mucositis accompanied by fresh onset lymphopenia, eosinophilia or atypical lymphocytosis, or unexplained hepatic/renal damage presenting weeks after starting HCQ. These may pose a difficulty if present at the puncture site for neuraxial/regional blocks. Also, the deranged total leucocytic count may complicate the decision to administer regional anesthesia.

HCQ is a substrate of several enzymes [cytochrome P4502C8 (CYP2C8), cytochrome P450 3A4 (CYP3A4/5), and cytochrome P450 2D6 (CYP2D6)] of the cytochrome pigment-450 (CYP450) family. HCQ can elevate metoprolol levels via CYP2D6 inhibition.[30,31] Pan-inhibitors of CYP450, such as cimetidine, on co-administration with HCQ may elevate HCQ levels.[32] Selective inhibitors of CYP3A4/5 (diltiazem, azithromycin, ciprofloxacin, among others) may also potentially raise serum-HCQ levels precipitating the HCQ toxidrome (cardiac arrhythmias, seizures, proximal muscle weakness). Treatment comprises early endotracheal intubation and IV diazepam boluses.[33]

HCQ-induced cardiomyopathy and heart failure[34] may accentuate the negative inotropic effect of anesthetic drugs. Pronounced fall in BP during anesthetic induction, especially with thiopentone and during the maintenance phase, particularly with halothane, may occur. Bispectral index (BIS)-guided administration of anesthetic agents in staggered doses is advisable.

Remdesivir

Remdesivir (GS-5734; Gilead Sciences Inc., Foster City, CA, USA), is an adenosine triphosphate analog, first described in the literature in 2016 as a potential treatment for the Ebola virus. In 2017, its activity against the coronavirus-family was demonstrated.[35,36]

On 1st of May, 2020, the US Food and Drug Administration granted an EUA[9] for remdesivir to treat hospitalized patients with suspected/confirmed COVID-19 with severe disease (oxygen saturation (SpO_2) ≤94% on room air/requiring supplemental oxygen/requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO). Remdesivir is administered by the intravenous route with a loading dose of 200 mg once daily in patients ≥40 kg or 5 mg/kg once daily in patients 35

Table 3: Anti corona virus-19 drugs and their interactions with each other and with anesthesia and peri-operative care drugs

NAME	DRUG-DRUG INTERACTIONS
HYDROXY CHLOROQUINE (HCQ)[5,6,15-23]	Anesthetics & Muscle relaxants: Propofol, Sevoflurane (QT prolongation) Thiopentone; Propofol; Halothane; Isoflurane; Sevoflurane (HCQ may potentiate negative inotropic effect) Analgesics and Opioids: Methadone; Papaverine; Tramadol (QT prolongation) Anxiolytics: Midazolam (Negative inotropy potentiation) Neuroleptics: Haloperidol; Droperidol; Sertraline; Imipramine; Chlorpromazine; Olanzapine; Clozapine (QT prolongation) Gastrointestinal drugs and Antiemetics: Ondansetron; Dolasetron; Promethazine (QT prolongation) Cimetidine (Inhibitors of CYP3A4 (CYP450) cause↑HCQ levels and toxicity) Inotropes, Vasopressors, Cardiac drugs: Amiodarone; Sotalol; Disopyramide; Quinidine; Procainamide (QT prolongation) Beta/Calcium-channel blockers; Class IA/IC antiarrhythmics (Negative inotropy potentiation); Digoxin [HCQ (P-Glycoprotien Inhibitor) prolongs Digoxin effects] Diltiazem (Inhibitors of CYP3A4 (CYP450) cause↑HCQ levels and toxicity) Amiodarone; Quinidine (Inhibitors of CYP450 (CYP2D6) cause↑HCQ levels) Emergency/Perioperative care drugs: Azithromycin; Clarithromycin; Ciprofloxacin, Gatifloxacin (QT prolongation) Erythromycin and Clarithromycin (CYP3A4) Ciprofloxacin (CYP1A2): ↑HCQ levels Clopidogrel Inhibitors of CYP450 (CYP2C8) cause↑HCQ levels and toxicity Hypokalemia (QT prolongation) Anti-COVID drugs: Ritonavir (QT prolongation)
Nitazoxanide (NTZ)[43-46]	Very High plasma protein binding (99.9%) so NTZ displaces other drugs Anesthetics and muscle relaxants: IV Lignocaine; Atracurium; Propofol Analgesics including opioids: All NSAIDS except aspirin Anxiolytics: Diazepam, midazolam, flurazepam, lorazepam, oxazepam, temazepam, Emergency/perioperative care drugs: Phenytoin, Carbamazepine; Valproic acid Warfarin, Chlorpropamide; Tolbutamide, tolazamide, glimepiride, glipizide
Remdesivir[34-41]	Remdesivir is a substrate for CYP2D6, CP3A and accumulates in renal dysfunction Anesthetics: Sevoflurane; Gallamine (Avoid nephrotoxic drugs) GI and anti-aspiration drugs: Cimetidine (Inhibitor of CYP3A4) Inotropes, cardiac drugs: Amiodarone; Diltiazem (Inhibitors of CYP2D6/CYP3A4) Emergency/Perioperative care drugs: Amikacin, gentamicin, tobramycin, neomycin, and amphotericin B (Nephrotoxic drugs) Erythromycin; Clarithromycin (Inhibitors of CYP3A4) Anti COVID drugs: Ritonavir (Inhibitor of CYP3A4)
Azithromycin[56-59]	Anesthetics & Muscle relaxants: Propofol, Sevoflurane (QT prolongation) Analgesics and Opioids: Methadone; Papaverine; Tramadol (QT prolongation) Neuroleptics: Haloperidol; Droperidol; Sertraline; Imipramine; Chlorpromazine; Olanzapine; Clozapine (QT prolongation) GI and Antiemetics: Ondansetron; Dolasetron; Promethazine (QT prolongation) Inotropes, Vasopressors, Cardiac drugs: Amiodarone; Sotalol; Disopyramide; Quinidine; Procainamide (QT prolongation) Emergency/Perioperative care drugs: Warfarin (Unknown mechanism) Hypokalemia (QT prolongation) Anti-COVID prophylaxis: BCG vaccine; MMR vaccine (Antibiotic effect); HCQ, Ritonavir (QT prolongation)
Ritonavir[53-55]	Ritonavir is a strong inhibitor of CYP3A4, is diabetogenic, hepatotoxic, and causes QT-prolongation; Avoid/reduce the dose of drugs metabolized by CYP3A4 Anesthetics & Muscle relaxants: Propofol, Sevoflurane (QT prolongation) L-bupivacaine, Lignocaine (CYP3A4 Substrates) Halothane, Isoflurane (Ritonavir is hepatotoxic) Analgesics and Opioids: Methadone; Papaverine; Tramadol (QT prolongation) Fentanyl, Naloxigol, Oxycodone, Naltrexone, (CYP3A4Substrates) Anxiolytics: Diazepam, Midazolam (CYP3A4 Substrates) Neuroleptics: Haloperidol; Droperidol; Sertraline; Imipramine; Chlorpromazine; Olanzapine; Clozapine (QT prolongation) GI and Antiemetics: Ondansetron; Dolasetron; Promethazine (QT prolongation) Inotropes, Vasopressors, Cardiac drugs: Amiodarone; Sotalol; Disopyramide; Quinidine; Procainamide (QT prolongation) Amiodarone Clopidogrel Diltiazem (CYP3A4 Substrates) Steroids: Prednisolone (CYP3A4 Substrate) Emergency/Perioperative: Erythromycin Amoxycillin (CYP3A4 Substrates) Metformin, Insulin (Ritonavir is Diabetogenic) Anti-COVID drugs; HCQ, Ivermectin, Remdesivir (CYP3A4 Substrates)

Contd...

Table 3: Contd...

NAME	DRUG-DRUG INTERACTIONS
Favipiravir (T-705)	Anesthetics: Propofol, ketamine (Favipiravir inhibits metabolism by CYP2C8) Analgesics: Morphine, ketorolac (Favipiravir inhibits metabolism by CYP2C8) Anti-aspiration: Ranitidine, cimetidine (Favipiravir inhibits metabolism by OAT1/SLC22A6) Famotidine (Favipiravir inhibits metabolism by OAT3/SLC22A8) Corticosteroids: Hydrocortisone (Favipiravir inhibits metabolism by OAT3/SLC22A8) Hydrocortisone, Dexamethasone (Favipiravir inhibits metabolism by P-glycoprotein) Perioperative drugs: Cephazolin (Favipiravir inhibits metabolism by CYP2C8) Anti-COVID-19 drugs: Ritonavir
Ivermectin[65-67]	Increased INR with oral anticoagulants by unknown mechanism: Warfarin Metabolized by CYP3A4 so avoid strong inhibitors of CYP3A4 Antihypertensive Diltiazem, Antiemetic Cimetidine, Antimicrobials: Erythromycin; Clarithromycin; Anti-COVI-19 drug: Ritonavir
Tocilizumab[70,71]	Tocilizumab reduces blood levels of CYP450 substrate drugs by CYP450 induction Anesthetics: Lignocaine Analgesics: Fentanyl, Sufentanil, methadone, naltrexone, oxycodone, buprenorphine Sedative-hypnotics: Diazepam, midazolam, alprazolam, clonazepam, triazolam, mephobarbital; GI and Anti-aspiration: Omeprazole Anti-COVID drugs: HCQ, Ivermectin, Remdesivir
Dexamethasone[72-76]	Dexamethasone is an inducer of CYP450 3A4 Muscle Relaxants/Reversal agent: Pancuronium, Rocuronium, Vecuronium, Neostigmine (unknown mechanism) Analgesics and opioids: Butorphanol, Fentanyl, Hydrocodone, Oxycodone, Buprenorphine, Codeine (Substrate of CYP450 3A4); NSAIDS (gastric ulcers) Cardiac Drugs: Amiodarone (Substrate of CYP450 3A4) Emergency and perioperative care: Insulin (Dexamethasone can vitiate diabetes control) Dexamethasone causes hypokalemia: Avoid drugs causing QT-prolongation

CYP-Cytochrome pigment; DDI-Drug-drug interactions; IV-Intravenous; NSAIDS-Non steroidal anti-inflammatory drugs

to 40 kg, followed by a maintenance dose of 100 mg once daily in patients ≥40 kg or 2.5 mg/kg once daily in patients 35 to 40 kg.[37,38] Patients not needing invasive mechanical ventilation/ECMO should be treated for 5 days, extending up to 10 days if they do not show improvement.[10] Patients requiring invasive mechanical ventilation or ECMO should be treated for 10 days.[10]

Most clinical trials have used a regimen of 200 mg once daily (OD) on day-1, followed by 100 mg OD for the next 9 days for moderate or severe COVID-19 infections.[10,38,39] Initial data indicates clinical benefit from just 5 days of remdesivir treatment in a few patients.[40,41]

Remdesivir is synthesized in a cyclodextrin-vehicle (12% sulfobutylether B-cyclodextrin sodium (SBECD), leading to toxic accumulation in patients with kidney dysfunction (eGFR <30 Ml/min/1.73m2).[42] Nephrotoxic drugs such as aminoglycosides (gentamycin) should not be co-administered with remdesivir. Although volatile anesthetics have a preconditioning renopreotective effect, sevoflurane should be avoided owing to the production of nephrotoxic inorganic fluorides and compound-A.[43] Remdesivir may elevate transaminase levels.

Category II (Other promising drugs in common use)

Nitazoxanide (NTZ)

Nitazoxanide (NTZ), is a 5-nitrothiazole derivative with proven efficacy against anaerobic bacteria, helminths, and protozoa.[44-46] NTZ has antiviral effects on the Hepatitis-C virus owing to enhanced interferon signaling and autophagy.[46] NTZ has anti-inflammatory and anticancer effects too.[44,45]

Tizoxanide (active metabolite of NTZ) is highly plasma-protein bound (>99.9%).[46,47] Hence, monitoring for adverse effects is essential when concurrently administering NTZ with other highly plasma-protein bound drugs [Table 3] with narrow therapeutic indices, in wake of competition for binding sites. For the same reason, dialysis is ineffective in NTZ-induced toxicity. Rapid hydrolytic metabolism to tizoxanide (desacetyl-nitazoxanide) occurs after ingestion followed by glucuronide conjugation. Tizoxanide has no significant inhibitory effect on cytochrome-P450 enzymes.[46,47]

Aspirin, diflunisal flurbiprofen ibuprofen, indomethacin, ketoprofen, methyl salicylate naproxen, piroxicam, phenylbutazone, comprise well-known NSAIDS clinically used for inflammation-related diseases, (rheumatoid arthritis) and chronic pain. All NSAIDS, except aspirin, are extremely highly plasma protein-bound. Efficacy and toxicity (gut bleed) of a particular dose may be enhanced by NTZ co-administration.[48,49]

Plasma-protein binding displacement drug interactions become clinically significant for low-clearance, low therapeutic-index drugs with a small volume of distribution.[50] Co-administration of drugs with high plasma-protein binding with NTZ can

increase the free-drug plasma levels, effects, and side-effects of these drugs by competitive displacement from protein binding sites (albumin, alpha-1acid glycoprotein (AAG), etc.)

Propofol is 48% plasma albumin-bound and 50% erythrocyte-bound.[51] NTZ may displace propofol from albumin and sharply increase free-propofol concentration in blood with consequent hemodynamic side-effects during induction. Propofol infusions for maintenance of anesthesia and ICU-sedation should be bispectral index (BIS)-guided. Target-controlled infusion (TCI)-pumps working on Marsh/Schneider pharmacokinetic models requiring only weight, height, and sex of the patient may over-deliver in such scenarios, as they disregard the propofol displaced from its plasma protein binding by NTZ. The maintenance infusion rate may need to be reduced to maintain the same target tissue concentration to avoid delayed awakening.

The benzodiazepine group of sedative-hypnotics contains several drugs (diazepam, flurazepam, lorazepam, oxazepam, quazepam, temazepam, midazolam, estazolam) with clinically significant interactions with NTZ. NTZ may increase the blood levels of these drugs by competitively displacing them from their plasma-protein binding sites causing excessive sedation and delayed awakening.[52]

Similarly, IV lignocaine for postoperative pain relief may be given by the PCA-pump, as pain relief would require a lower amount of drug to be infused for the same plasma concentration.[52]

In diabetics, discontinuation of oral hypoglycemics (chlorpropamide; tolbutamide, tolazamide, glimepiride, glipizide, glyburide) and switching over to insulin should be done in all patients on NTZ to avoid dangerous hypoglycemia arising out of increased free plasma fraction of these drugs due to displacement from binding sites of these highly plasma-bound drugs.[53]

The situation is more complex in diabetic-cancer patients undergoing chemotherapy because NTZ displaces highly plasma-protein bound anticancer drugs (methotrexate, cisplatin, and vinblastin) from their binding sites causing severe toxicity.[48] Cyclosporine, mycophenolate, and tacrolimus are highly protein-bound immunosuppressants and may reach toxic levels after being displaced by NTZ.

AAG is a low capacity protein and its binding-site saturation occurs by drugs in therapeutic concentrations. AAG levels significantly increase in cancer, renal failure, myocardial infarction, rheumatoid arthritis, and intensive care patients. Lignocaine, quinidine, and alfentanil strongly bind to AAG.[48] Unbound-lignocaine concentration decreases in uremic patients, who have twofold higher AAG levels, whereas the unbound concentration of serum albumin-binding drug diazepam increases due to a decrease in albumin levels in uremic patients. Higher binding of lidocaine and alfentanil also correlates well with increased AAG levels in myocardial infarction patients.

Ritonavir

Ritonavir (Abbott Laboratories, Lake Bluff, Illinois, US) is a protease-inhibitor type of antiretroviral (anti-HIV) drug currently under empirical use for COVID-19 treatment. Ritonavir may cause dose-related QT-prolongation and must not be coadministered with other such drugs.[54] Ritonavir is a strong inhibitor of CYP3A4 and drug transporter P-glycoprotein and may increase blood levels of fentanyl, diazepam, amiodarone, HCQ, remdesivir, ivermectin, and other drugs metabolized by these pathways.[55,56] Resultant increased plasma fentanyl concentrations could cause delayed awakening after anesthesia, potentially fatal respiratory depression, extreme sedation, and bradycardia. Conversely, discontinuation of ritonavir in surgical ICU patients could reduce plasma fentanyl levels, leading to diminished opioid efficacy, and even withdrawal syndrome in patients with physical dependence on fentanyl. We suggest lower benzodiazepine (diazepam, midazolam, clonazepam, alprazolam) dosages in patients on ritonavir, or administering drugs not metabolized by the CYP3A4 pathway (lorazepam, oxazepam, temazepam). Ritonavir elevates lignocaine and L-bupivacaine levels.[56] Similarly, amiodarone toxicity with ventricular arrhythmias may occur on co-administration if amiodarone dosage is not reduced. There is a five times higher risk of sudden cardiac death if erythromycin/amoxicillin is co-administered with ritonavir. Ritonavir causes hyperglycemia and hampers the efficacy of insulin and other antidiabetics.[56]

Azithromycin

Azithromycin (Pfizer Inc., Manhattan, New York City, USA) causes QT-prolongation. Concomitant use with HCQ and other drugs augmenting QT-prolongation should be avoided.[57] Co-administration of azithromycin with tramadol may, albeit rarely, lead to a potentially life-threatening irregular heart rhythm.[58] Patients with the congenital long-QT syndrome, conduction abnormalities, or electrolyte disturbances (hypokalemia/hypomagnesemia resulting from severe/prolonged diarrhea/vomiting) are more susceptible. Concomitant use of two or more QT-prolonging drugs should be avoided. Certain opioids (tramadol; methadone) and also propofol are implicated in QT-prolongation.[58,59]

BCG vaccine (live, attenuated *Mycobacterium bovis*) given for COVID-prophylaxis may be rendered ineffective if

used concomitantly with antibiotics including azithromycin. Co-administration with azithromycin may occasionally enhance the hypoprothrombinemic effect of warfarin by an unknown mechanism.[60] Azithromycin does not inhibit CYP450 enzymes.

Favipiravir

Favipiravir (Fujifilm Toyama Chemical Co. Ltd; Tokyo, Japan) is converted into an active phosphoribosylated form which is a substrate of viral RNA-polymerase. Favipiravir was approved for COVID-19 treatment in China (March 2020) based on preliminary data from clinical studies.[61] Co-administration with interferon-α aerosol inhalation (5MU twice daily) may increase efficacy against COVID-19.[62] Favipiravir significantly inhibits acetaminophen sulfate formation without impacting acetaminophen glucuronide formation.[63] Maximum daily acetaminophen dosage should be restricted to 3 g in patients taking favipiravir. Favipiravir may reduce ketamine, propofol, ketorolac, diclofenac, buprenorphine, warfarin, amiodarone, diltiazem, and omeprazole metabolism.[64] Excretion of ranitidine, famotidine, digoxin, hydrocortisone, and dexamethasone is reduced. The serum concentration of morphine, dabigatran, and mannitol is increased by favipiravir. Cimetidine, ondansetron, and diltiazem inhibit favipiravir metabolism.[64] Although one case report incriminates favipiravir in QT-prolongation, a Japanese study on 56 subjects rules this out.[65]

Ivermectin

Ivermectin is a broad-spectrum antiparasitic agent with antiviral properties. ICMR is reviewing claims of Bangladeshi scientists regarding ivermectin-doxicycline combination for swift relief from COVID-19.[66] Co-administration with CYP3A4-inhibitors [Table 3] may increase plasma ivermectin levels and hence adverse effects.[67] Coadministration of warfarin with ivermectin may, albeit rarely, cause increased international normalized ratio (INR) by an unknown mechanism.[68]

Tocilizumab

Tocilizumab (Actemra; Genentech, South San Francisco, CA.) is an interleukin-6 (IL-6) receptor monoclonal antibody used as a disease-modifying drug for rheumatoid arthritis.[69] It is another potential anti-SARS-CoV-2 drug.[11]

Down-regulation of synthesis of hepatic cytochromes P450 (CYP450) enzymes occurs during infection and chronic inflammation, owing to increased cytokine (including IL-6) levels. Tocilizumab targets IL-6 and may restore/normalize CYP450 enzyme levels. Hence, tocilizumab may decrease plasma concentrations and effects of drugs that are CYP450 substrates. These drugs may have a narrow therapeutic index (antiarrhythmics, anticonvulsants, immunosuppressants, theophylline) or the decrease in their plasma levels may be significant/undesirable (oral contraceptives, benzodiazepines, opioids).[70] Caution is advised in the form of clinical/laboratory monitoring following the initiation/withdrawal of tocilizumab and the dosage of the CYP450 substrates adjusted accordingly. Effects of tocilizumab on CYP450 may persist for several weeks after stopping therapy.[71] From an anesthesiologist's perspective reduced blood levels of opioids (fentanyl, sufentanil, methadone, naltrexone, oxycodone), lignocaine, and sedative-hypnotics (diazepam, midazolam, alprazolam, clonazepam, triazolam, mephobarbital)[70,71] due to tocilizumab co-administration may hamper intra- and postoperative analgesia and ICU-sedation. Omeprazole levels show a 28% reduction after a single dose of tocilizumab.[71]

Tocilizumab by the same mechanism may reduce the efficacy of other drugs (HCQ, remdesivir, zinc) concomitantly being used for COVID-19 prophylaxis/treatment.

Dexamethasone

Most anesthesiologists are already familiar with corticosteroids including dexamethasone. Hence only the important drug interactions with anesthetic agents are briefly summarized here. Dexamethasone is an inducer of CYP450-3A4[72] and hence may reduce the plasma concentrations of opioids (butorphanol, fentanyl, hydrocodone, oxycodone, buprenorphine, codeine) metabolized by this isoenzyme. Reduced efficacy/withdrawal symptoms may occur following the addition of dexamethasone to the narcotic pain regimen. Discontinuation of dexamethasone may cause overdose and respiratory depression by increasing plasma opioid concentration. Dexamethasone by an unknown mechanism reduces the effects of pancuronium, rocuronium, vecuronium, and neostigmine.[73-75] Amiodarone is an important emergency use drug whose hepatic metabolism is increased and effectively reduced by dexamethasone coadministration.[75] Anti-emetic doses of dexamethasone interfere with glucose metabolism and increase blood sugar levels in diabetics and nondiabetics for up to 4 h and reduce the action of insulin.[75] It delays the healing of gastrointestinal erosions caused by NSAIDS.[76] Dexamethasone may cause hypokalaemia and must not be coadministered with drugs causing QT-prolongation.

Conclusion

The purported anti-COVID-19 drugs have several drug interactions with anesthetic agents and drugs commonly used for perioperative care. Anesthesiologists, intensivists, and the perioperative care team should use this knowledge to avoid

unnecessary multiple drug therapy and optimize patient-care in corona times.

Summary

- *Purported anti-COVID drugs have clinically relevant interactions with anesthetic agents, chemotherapeutic agents, and drugs used in perioperative care*
- *The terminal half-life of HCQ being 1–2 months, discontinuation of HCQ 5–7 days before surgery in the PAC clinic may not help.*
- *Co-administration of two or more drugs that cause QT-prolongation (HCQ, azithromycin, ritodrine, propofol, sevoflurane, tramadol, ondansetron, etc.) should be avoided.*
- *HCQ may accentuate the negative inotropic effect of anesthetic induction agents.*
- *Remdesivir accumulates in renal impairment patients owing to its cyclodextrin carrier, and nephrotoxic drugs such as gentamycin, gallamine, and sevoflurane should be avoided in these patients.*
- *NTZ displaces highly plasma protein–bound anticancer drugs (methotrexate, cisplatin, vinblastin) from their binding causing severe toxicity.*
- *Ritonavir is a strong inducer of CYT P450-3A4 isoenzyme and drugs metabolized by this pathway (fentanyl, diazepam, amiodarone, HCQ, remdesivir, ivermectin) may increase to toxic levels.*
- *Effects of tocilizumab on CYP450 may persist for several weeks after stopping therapy which may hamper fentanyl and midazolam-based postoperative analgesia/ICU sedation regimen.*
- *Dexamethasone is an inducer of CYP450 3A4 and hence may reduce the plasma concentrations of opioids and also may reduce effects of pancuronium, rocuronium, vecuronium, and neostigmine by an unknown mechanism.*

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Conflicts of interest
There are no conflicts of interest.

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