Clinical Pharmacology Considerations for Developing Small-Molecule Treatments for COVID-19

Priya Brunsdon, PharmD, Bhawana Saluja, PhD, and Chandrahas Sahajwalla, PhD, FCP

Abstract

Numerous drugs are being investigated for the treatment of COVID-19, including antivirals and therapies targeting complications related to COVID-19. The clinical presentation of COVID-19 varies from mild fever, cough, and dyspnea in the early stages of disease to severe complications such as acute respiratory distress syndrome, systemic hyperinflammation, and sepsis. A thorough understanding of the disease pathogenesis and the disease complications is essential to developing effective therapies to treat this potentially life-threatening disease. This review offers key clinical pharmacology considerations involved in the development of small molecules for the treatment of COVID-19. They are based on the major observed disease complications that impact drug absorption, distribution, metabolism, and elimination. We also address considerations regarding potential drug interactions, alternative routes and methods of administration, and dosing in patients on hemodialysis.

Keywords
clinical pharmacology, COVID-19, pharmacology, review, SARS-CoV-2

The respiratory disease (COVID-19) that was first reported in Wuhan, China, in December 2019 is caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2).1 COVID-19, which was declared a pandemic by the World Health Organization in March 2020, has been characterized by a rapid spread and profound impact to public health worldwide.2 As of June 18, 2020, more than 8,242,999 reported cases and 445,535 deaths globally were attributed to the COVID-19 outbreak.3 Mild cases of the disease may present only with cough, fever, myalgia, and malaise. Gastrointestinal symptoms include nausea, diarrhea, and anorexia. Abnormal symptoms such as total loss of taste and smell also have been reported.4 In severe cases of COVID-19, complications can include sepsis and septic shock, multiorgan failure, and acute kidney injury. In addition, observational studies detailing neurological symptoms of the disease, along with reports of large-vessel stroke in young patients indicate that the disease manifests throughout the body.5,6

Infection with SARS-CoV-2 begins with viral binding to airway epithelial cells that express angiotensin-converting enzyme 2 (ACE2).7 One proposed mechanism for antiviral drugs involves blocking viral binding to ACE2, thereby blocking viral entry into host cells. Following viral infection, a local immune response is triggered, which can be beneficial to clearing the infection. However, the response can become dysregulated, resulting in cytokine release syndrome (or “cytokine storm”), which is an overproduction of proinflammatory cytokines such as interleukin (IL)-6, IL-10, and tumor necrosis factor. Numerous biologics and small molecules with immunomodulatory effects have been proposed as investigational therapies targeting the inflammatory response or cytokine storm. Therapies for other complications associated with COVID-19, such as thrombosis, also have been proposed. At the time of writing, no specific treatment for COVID-19 had been approved by the U.S. Food and Drug Administration (FDA), and most drugs sought for evaluation of efficacy are being repurposed from other clinical indications. This review will offer key clinical pharmacology considerations for developing...
small molecules for the treatment of COVID-19 based on the major disease complications that impact drug absorption, distribution, metabolism, and elimination (ADME). We also will address special scenarios such as changing the method of drug administration because of intubation/ventilation and hemodialysis. Table 1 highlights physiological changes and complications observed in COVID-19 patients and their associated impact on drug pharmacokinetics. Although biologics have distinct drug development considerations, we discuss issues related to COVID-19 that specifically impact clinical pharmacology for small-molecule drugs.

### Clinical Progression and Complications of COVID-19

Each stage of COVID-19 presents unique clinical pharmacology considerations for developing COVID-19 therapeutics. The major symptoms and clinical progression of COVID-19 can be described within the framework of a proposed staging scheme by Siddiqi et al.\(^8\) The first stage of early infection occurs immediately after inoculation and is characterized by mild, nonspecific symptoms such as fever and cough. At this stage, patients normally are treated on an outpatient basis with supportive care. Antiviral therapy may be most useful at this stage to diminish the escalation of viral replication. No specific antivirals have been approved for COVID-19; however, remdesivir received an emergency use authorization (EUA) by the FDA for the treatment of COVID-19 in adults and children who are hospitalized with severe disease.\(^9\) Oral formulations of chloroquine phosphate and hydroxychloroquine sulfate also received an EUA for the treatment of COVID-19 on March 28, 2020, which was later revoked on June 15, 2020, because of new information indicating the drugs may not be effective in treating COVID-19.\(^10\)

As the viral load in the body increases, pulmonary symptoms worsen, and viral pneumonia develops. Stage 2, or moderate disease severity, can be identified by an increase in pulmonary inflammation and usually results in hospitalization. Although most people with COVID-19 experience mild or uncomplicated illness, approximately 15% of patients develop severe disease,
and 5% require admission to an intensive care unit. In the later parts of this stage, development of hypoxia can result in the need for mechanical ventilation. Patients who develop severe cases of COVID-19 can develop respiratory infections associated with acute lung injury and acute respiratory distress syndrome (ARDS). Management of ARDS can require supplemental oxygen, mechanical ventilation, and endotracheal intubation.

Stage 3, the most severe form of COVID-19, is marked by systemic hyperinflammation and often the elevation of inflammatory cytokines. Possible complications include cytokine storm, septic shock, acute kidney injury, and multiorgan failure. Of major concern is sepsis, defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection." In 1 study, septic shock, which is distinguished by persistent hypotension, elevated serum lactate levels, and increased mortality, was a complication in about 6% of severely ill COVID-19 patients. Both sepsis and septic shock result in a complex set of physiological changes that can impact the ADME of drugs. Most repurposed investigational drugs that target complications associated with the severe stages of disease, such as hyperinflammation, have not previously been evaluated in patient populations that routinely are septic or critically ill. The remainder of this review will cover the physiological changes and clinical pharmacology considerations for selection of dosing in severe COVID-19 patients and will address special dosing situations.

**Absorption**

Critically ill COVID-19 patients may have altered rates and/or extents of drug absorption through the gastrointestinal (GI) tract because of hypoperfusion, delayed gastric emptying, and use of vasopressors. In patients with sepsis or septic shock, blood is shunted away from peripheral tissues toward vital organs in response to pronounced systemic hypotension. Poor blood flow to the gut combined with delayed gastric emptying can slow or allow for incomplete absorption of oral drugs. Delayed absorption consequently can slow a drug's expected onset of action.

Vasopressors are routinely initiated in septic shock patients with hypotension that is unresponsive to fluid resuscitation. In a study of 393 consecutive COVID-19 patients admitted to New York hospitals, 33% of all patients (and 95% of subjects who required mechanical ventilation) received vasopressor support. Vasopressors, such as norepinephrine, increase vasoconstriction to produce an increase in mean arterial pressure and improve perfusion to organs. Several studies report improved splanchnic blood flow following vasopressor therapy. Whether these changes in splanchnic blood flow will translate to meaningful increases in oral drug absorption, however, is not entirely clear in light of conflicting results from previous studies. Drugs administered intramuscularly or subcutaneously also can produce unpredictable alterations in absorption because of a combination of decreased perfusion of the muscle tissue and possible vasopressor therapy.

The potential for decreased or delayed absorption and variability associated with vasopressor therapy should be considered during the drug development process, especially with drugs for which the time to onset of action is of critical importance. The possibility of intravenous administration should be examined to reduce the variability associated with altered absorption of oral, intramuscular, and subcutaneous drugs. The safety margin and expected exposure following conversion to the intravenous route also should be considered when selecting doses for intravenous bolus or infusion.

**Distribution**

Intravenous fluid resuscitation is a first-line therapy for the treatment of sepsis-induced hypoperfusion. Infused fluids can increase the volume of distribution for water-soluble drugs, such as beta-lactams and aminoglycosides, leading to unexpectedly lower serum drug concentrations. For example, beta-lactam antibiotics administered in patients with increased volumes of distribution may not achieve therapeutic plasma concentrations, and consequently, risk treatment failure. In a pharmacokinetic study of critically-ill patients during and after fluid resuscitation therapy while receiving treatment with gentamicin, the apparent volume of distribution was 48% greater during initial fluid resuscitation therapy, therefore necessitating higher doses of gentamicin. Therapeutic drug monitoring has been employed with antibacterial agents to address complications posed by increased volumes of distribution, although that approach likely is not feasible in studies with investigational drugs. For water-soluble investigational therapies that are intended for administration in the severely ill COVID-19 population, thought should be given to targeting serum drug concentrations and the drug's exposure-response profile when determining if increased doses would be beneficial for patients receiving intravenous fluids.

Hypoperfusion of tissues in septic patients can decrease the efficacy of hydrophilic medications at the site of action. Under septic conditions, reduced perfusion of peripheral tissues can be caused by an array of hemodynamic changes. Reduced perfusion and therefore delivery of the drug via the blood, can impede the ability of water-soluble medications to reach the desired site of action. In such cases, systemic drug
concentrations may not be indicative of the drug concentration at the site of action. Higher systemic plasma concentrations of hydrophilic medications should be considered to achieve target concentrations in the targeted tissues.

Hyperinflammatory and septic conditions can increase or decrease acute-phase plasma protein levels, impacting drug binding, volumes of distribution, and free drug fractions. Albumin and α1-acid-glycoprotein (AAG) are 2 major drug-binding plasma proteins. Levels of negative acute-phase proteins such as albumin decrease in conditions of inflammation, possibly leading to initial increases in free drug plasma fractions for drugs extensively bound to albumin. Positive acute-phase proteins such as AAG and C-reactive protein increase during situations of infection or inflammation. Hundreds of drugs, including propranolol, imatinib, and vinblastine, have been identified as binding to AAG. Increase in production of these proteins will similarly increase drug binding and decrease free drug fractions. These changes in protein levels were observed in a retrospective analysis of 99 COVID-19 patients in Wuhan, China, where 98% of admitted patients had decreased albumin levels and 86% had increased C-reactive protein levels. The clinical impact of these potential changes in free drug fractions on investigational therapies that are highly protein-bound is an important consideration when empirically selecting doses for critically ill COVID-19 patients.

**Metabolism**

Septic conditions and the development of organ dysfunction in COVID-19 patients can affect the metabolic capacity of the liver, leading to alterations in drug exposure. Drugs that are inactivated through metabolism can have prolonged exposure because of lowered enzymatic capacity of the liver and decreased hepatic blood flow in septic conditions. Prodrugs that are metabolized by cytochrome P450 enzymes to active metabolites may conversely experience slowed or incomplete conversion, lessening the therapeutic exposure. The hepatic expression and activity of cytochrome P450 enzymes is decreased in situations of acute inflammation, possibly because of their direct downregulation mediated by proinflammatory cytokines. In addition, decreased hepatic blood flow reduces the clearance of drugs with high hepatic extraction ratios. Use of vasoressors to increase mean arterial pressure in sepsis further potenititates the decrease in hepatic blood flow. In addition, because in most cases only unbound drug is capable of being metabolized, the changes in protein binding described previously can also alter the free drug concentration.

**Elimination**

Renal filtration is the primary route of excretion for many drugs. These drugs carry a risk of accumulation in patients with renal impairment and often require dose reductions. Drug exposure of investigational COVID-19 therapies should be estimated in subjects with renal impairment based on available data to inform dosing in this population. In a survey of labels for drugs approved between 2016 and 2018, dosing information for patients with severe renal impairment or kidney failure was only available for about 50% of the drugs. If a change in exposure is unknown because of lack of clinical data and cannot reliably be estimated based on the drug’s elimination pathway, subjects with renal impairment may be restricted from enrollment in studies based on the severity of impairment. They may even be excluded if higher or prolonged drug concentrations pose significant safety concerns.

Excluding these subjects from studies, however, only addresses those with prior known renal impairment on enrollment and not those who develop impairment as part of the COVID-19 disease course. In a study of 5449 COVID-19 patients in New York, 37% developed acute kidney injury (AKI). Increased age and comorbidities such as diabetes mellitus and hypertension were determined to be predictors of AKI. Proposed mechanisms for the development of AKI in COVID-19 patients include cytokine damage and intrarenal inflammation, renal hypoperfusion, fluid expansion leading to renal vein congestion, and direct cytopathic effects of the virus on kidney cells. Sufficient monitoring plans for assessing renal function throughout the treatment period of a clinical trial are needed to detect the development of AKI and implement any required dose adjustments or dose discontinuation based on the drug’s toxicity profile.

The standard therapies indicated for patients with AKI, namely, continuous renal replacement therapy (CRRT) and intermittent hemodialysis, can pose obstacles for the administration of investigational therapies. In an observational study from China, 5% of severe COVID-19 patients required the use of CRRT. Hemodialysis removes waste, toxins, and drugs from the bloodstream by diffusion through a dialyzer membrane. Drugs with low molecular weight, low volume of distribution, and high solubility carry more risk of being cleared by hemodialysis. One possible dosing strategy for these drugs is to administer the dose following the end of hemodialysis. Drugs with higher molecular weight diffuse more slowly and in the case of therapeutic proteins are too large to pass through the dialyzer membrane. These drugs may be dosed irrespective of dialysis because drug exposure would not be impacted by a dialysis session. Furthermore,
only unbound drug fractions are capable of being dialyzed; therefore, drugs with low protein binding will undergo greater clearance from dialysis. The impact of hemodialysis on drug exposure is assessed infrequently during the drug development process, and clinical data for dosing during hemodialysis is unlikely to exist prior to the initiation of studies in COVID-19 patients. However, if an investigational therapy is at risk of clearance from hemodialysis based on its physiochemical properties and drug binding, timing of drug administration and hemodialysis needs to be spaced appropriately. If hemodialysis must resume following drug administration, the time required for absorption and distribution of the drug to the site of action and the expected time course of pharmacologic effects must be weighed.

**Drug Interactions**

Drugs under investigation for the treatment of COVID-19 will need to be administered on top of the standard of care at study sites. For hospitalized COVID-19 patients, this may include antivirals, antibacterial agents, acid-reducing agents (as indicated for stress ulcer prophylaxis), deep vein thrombosis prophylaxis, and other supportive care agents such as vasopressors or sedatives. Other investigational therapies such as remdesivir also may be included in the standard of care. In addition, medications for preexisting comorbidities also may require continued dosing in the hospital setting.

Pharmacokinetic (PK) drug interactions could impact the efficacy either of the standard of care or of the investigational drug. For example, routine use of proton pump inhibitors in intubated patients, as indicated for stress ulcer prophylaxis, increases gastric pH and can reduce the solubility of drugs that require an acidic environment for absorption. In addition to pharmacokinetic interactions, potential pharmacodynamic (PD) interactions need to be assessed. Pharmacodynamic interactions can cause additive or opposing physiological effects to occur. For instance, azithromycin is a QT-prolonging drug that has been previously studied for treatment of COVID-19. The possibility for additive QT prolongation with investigational drugs requires assessment through adequate electrocardiogram-monitoring plans.

Other types of PD interactions can include competition or agonism at the target receptors through competitive and noncompetitive inhibition or allosteric modulation. Additional possibilities include synergistic or antagonistic effects related to the second-messenger systems or downstream effects. A rapidly changing clinical landscape for the treatment of COVID-19 means that drug interaction potential needs to be assessed using the most up-to-date standards of care. However, background medications or standards of care that include other investigational therapies may create difficulty when interpreting efficacy data, so their concomitant use should be carefully considered.

**Route of Administration**

Most drugs proposed for the treatment of COVID-19 are administered through the oral or intravenous route. Given the sites of viral proliferation, however, delivery of antiviral drugs via inhalation may provide increased efficacy while reducing systemic risks. In an analysis of 9 COVID-19 patients with mild symptoms, high concentrations of SARS-CoV-2 RNA were detected in the upper respiratory tract and lungs, as measured by pharyngeal swabs and sputum samples. Live virus was isolated from the pharyngeal swabs, signaling active viral replication in the upper respiratory tract during the first week following the onset of symptoms. The virus was not detected at any time in blood or urine, and live virus was not detected in stool. Drug delivery via inhalation, especially early in the disease course, could therefore confer the benefit of targeted antiviral activity at the site of viral replication, namely, the upper respiratory tract, while reducing systemic exposure.

Investigational antivirals such as remdesivir may potentially benefit patients in inhaled dosage forms. Remdesivir is currently administered via intravenous infusion, restricting its use to hospitalized patients. Other constraints for remdesivir based on renal impairment are detailed in the EUA. An inhaled formulation of remdesivir could expand its availability to patients who have less severe symptoms, are early in the disease course, or are otherwise ineligible for treatment with intravenous remdesivir. Lower systemic exposure after drug inhalation may also eliminate the need to exclude patients with renal impairment.

Commonly used inhalation devices include metered-dose inhalers, dry powder inhalers, and nebulizers. In COVID-19 patients, drug delivery by metered-dose inhalers or dry powder inhalers could be negatively affected by pulmonary symptoms that limit the force of inhalation, improper patient technique, and an inability to coordinate breaths with actuation. For these reasons, nebulizers may be the most practical choice for drug delivery via inhalation in COVID-19 patients, as it only requires tidal breathing without coordinated inhalation. In studies of chronic obstructive pulmonary disease patients, nebulizers were found to have similar efficacy to metered-dose and dry powder inhalers when properly used. Drawbacks of treatment of nebulizers include high intersubject variability, which may be because of differences in breathing pattern or nebulizer device type. In addition, nebulizers can increase the risk of SARS-CoV-2 transmission to study
Developers of inhaled formulations that are intended to reach the site of action should consider the drug’s individual characteristics, such as particle size. In addition, considerations in determining an appropriate inhalation device could include patients’ ability to use proper inhalation technique, to effectively inhale given their progression of pulmonary symptoms, and the added risk to health care providers.

**Method of Administration**

Progression of COVID-19 can result in respiratory deterioration, leading to ventilator use. From a study of 1099 COVID-19 patients, 39% of patients with severe disease required mechanical ventilation. Mechanical ventilation and endotracheal intubation often prevent drug administration through the typical oral route. Enteral feeding tubes such as nasogastric (NG) tubes must be employed for oral medications if another method or route of drug administration is not available. Crushing or dissolving of solid oral dosage forms can result in issues with safety/toxicity or efficacy.

Increased drug absorption can put the patient at risk for toxicity-related adverse events. A common medication error involves improper crushing or dissolving of modified-release formulations, leading to dose dumping. Decreased first-pass metabolism can occur when feeding tubes bypass a portion of the gastrointestinal tract and terminate in the jejunum. In this case, drugs with high first-pass metabolism, such as opioids and beta-blockers, would have increased bioavailability.

Decreased drug absorption, resulting in decreased efficacy, also may occur when modifying an oral drug for administration via feeding tube. Enteric coatings of tablets protect the drug substance from breakdown by stomach acids, allow for absorption in the small intestine, and/or prevent gastric irritation. Crushing or dissolving these tablets for tube administration removes the protective coating, likely reducing its systemic absorption and increasing the potential for gastric adverse events. In addition, enteral feeding solutions increase the gastric pH, which can reduce the absorption of drugs with pH-dependent solubility.

Small-bore feeding tubes are prone to obstruction or clogging by powdered tablets or capsules and also can result in decreased drug absorption. Adsorption or adherence of the drug to the feeding tube also can reduce the administered dose. Flushing feeding tube lines before and after drug administration may prevent clogging, but study protocols need to provide detailed instructions on volume and timing to ensure consistency in administration. Feeding tubes can terminate in the stomach, duodenum, or jejunum. Their placement in the jejunum can decrease overall absorption time in the GI tract or impact the absorption of drugs that require an acidic gastric environment.

Investigational study protocols for COVID-19 oral therapies should assess alternative routes or methods of administration if medications cannot be taken by mouth. If administration via feeding tube is proposed, detailed instructions to ensure consistent drug administration should be established. Dosing plans need to be based on the physiochemical properties of the drug (eg, solubility), site of absorption, and formulation.

**Discussion**

Severe cases of COVID-19 are associated with numerous complications and physiological changes that have the potential to alter investigational drug ADME. When investigating new therapies to treat COVID-19, these alterations need to be evaluated carefully to determine initial dosing in COVID-19 patients, as well as the need for dose modifications or drug discontinuation. The average time from COVID-19 symptom onset to death is estimated to be 18 days. Most therapeutic agents are proposed for investigation in moderate to severe COVID-19 patients, leaving a limited window of time to determine appropriate dosing based on the most impactful physiological alterations in a patient.

Assessing potential drug interactions in COVID-19 patients is an especially arduous task, given rapidly evolving therapeutic knowledge and treatments. Concomitant administration of other investigational therapies may create difficulty in interpreting efficacy data; therefore, permitted and prohibited background therapies should be selected carefully based on potential PK and PD interactions with the investigational drug.

Existing population pharmacokinetic models can be used to simulate exposure of new doses and/or regimens and support initial dosing. However, many drugs proposed for evaluation in COVID-19 patients are being repurposed from indications in which the patient population is not critically ill. Some information can be extrapolated from other patient populations for empiric dosing, but blood sample collection for analysis of PK and PD end points in COVID-19 patients is critical to characterizing the drug exposure in that population and optimizing dosing in future studies. A joint statement from major pharmacologic societies also describes this need to measure drug concentrations to develop PK models in COVID-19 patients as part of a core clinical pharmacology principle guiding development of COVID-19 treatments.

Numerous drugs have been proposed to treat COVID-19, addressing both complications and direct antiviral activity. The many clinical pharmacology considerations discussed in this review, such as alterations...
in absorption and distribution, relate to initial dose selection in the COVID-19 population. Other issues, such as the development of AKI or NG tube administration of drugs, need to be specified in proposed protocols for investigational drugs. The FDA’s Office of Clinical Pharmacology has frequently commented on certain protocol areas that need to be addressed, such as the lack of a dosing plan for hemodialysis. Although by no means all-encompassing, following are samples of our common advice regarding investigational protocols:

• “The development of acute kidney injury requiring hemodialysis has been reported as a possible complication during the disease progression of COVID-19. Address how the dose and regimen will be modified in the event that patients require hemodialysis (eg, dosing after hemodialysis, treatment discontinuation).”

• “Conditions permitting, you should collect blood samples for PK assessment in the proposed study in order to characterize PK in the COVID-19 population and better inform dose selection in future studies.”

• “Detailed dosing instructions for the scenario that patients develop the need for intubation should be included in the protocol.”

• “All likely concomitant medications or medications administered as part of the Standard of Care should be assessed for drug interaction potential with the investigational drug. Dose adjustments or appropriate monitoring plans should be based on the known drug interaction potential and toxicity profile of the drug.”

The totality of evidence should be considered for inclusion of patients with compromised organ impairment and other comorbidities. Hospitalization, critical-illness, and mortality are higher in patients with various comorbidities. Most notably, diabetes, obesity, older age, and hypertension are the risk factors most strongly associated with COVID-19 hospitalization. Exclusion of these subjects from clinical trials may delay availability of drugs to vulnerable populations. Reports from New York City and Chicago also show that Black and Latino COVID-19 patients have death rates that are 2 to 3 times higher than white patients. Current FDA recommendations propose including subjects with high-risk comorbidities, older adults, and racial and ethnic minorities in clinical trials. Existing clinical and nonclinical ADME data along with the safety profile of the drug should be leveraged to select populations for inclusion. A suitable approach for inclusion of subjects with organ impairment or other risk factors must be determined on a case-by-case basis. One possible method is to include these patients in a stepwise manner with appropriate stopping criteria for adverse events or toxicity. Early collection of PK/PD data in these patients could then inform dosing in more severe patients. The nature and severity of anticipated safety events, whether they are monitorable, and whether dose reductions are possible also need to be weighed in the decision-making process.

COVID-19 has proven to be a unique drug development scenario because the rapid spread of severe illness has resulted in an urgent compression of the drug development timeline. Clinical pharmacologists now have an added responsibility to make rapid, informed decisions, often based only on preliminary or incomplete knowledge of the drug and pathophysiology. However, this scenario also creates an opportunity for the clinical pharmacology community to positively influence the strategic, expedited development of drugs that are vital to combating a public health crisis.

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Conflicts of Interest

The authors have declared no conflicts of interest for this article.

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