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Drugs in COVID-19 Therapy and Their Pharmacokınetıcs

COVID-19 Tedavisinde Kullanılan İlaçlar ve Farmakokinetiği

Esra Demirtürk[1]

[1]Çukurova University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Adana, Turkey

ABSTRACT

Pharmacokinetics deals with all the factors that control this process, including the degree and rate at which a drug enters the body, is distributed, reaches its site of action, exerts its effect and is excreted. It also examines the time-dependent changes in the level of the drug in different compartments during this process. While the primary aim of pharmacokinetics is to determine the variables affecting patient- and drug-related kinetic parameters, the secondary aim is to define the kinetic parameters in the dose-concentration-time relationship. Therefore, the pharmacokinetic parameters of any drug used in emergencies or in special populations are instructive. In the context of COVID-19, understanding the pharmacokinetics of the medications used is crucial in order to achieve optimal therapeutic outcomes. This knowledge helps in determining the appropriate dosage, frequency of administration, and duration of treatment for COVID-19 patients. Pharmacokinetics also plays a role in understanding potential drug-drug interactions and the likelihood of adverse drug reactions. Furthermore, pharmacokinetic studies can aid in the development of new treatment strategies and therapeutic interventions for COVID-19. This article describes the key pharmacokinetic parameters for favipiravir, remdesivir, lopinavir, ritonavir, chloroquine and hydroxychloroquine, which are recommended for use in the treatment of COVID-19. This study will provide a knowledge base on the pharmacokinetics of various COVID-19 drugs.

Keywords: COVID-19, pharmacokinetics, favipiravir, remdesivir, lopinavir, ritonavir

ÖZET

Farmakokinetik, bir ilacın vücuda girme, dağılma, etki alanına ulaşma, etkisini gösterme ve atılma derecesi ve hızı dahil olmak üzere bu süreci kontrol eden tüm faktörlerle ilgilenir. Ayrıca bu süreç boyunca ilacın farklı kompartımanlardaki seviyesinin zamana bağlı olarak nasıl değiştiğini de inceler. Farmakokinetiğin birincil amacı hasta ve ilaçla ilgili kinetik parametreleri etkileyen değişkenleri belirlemek iken, ikincil amacı doz-konsantrasyon-zaman ilişkisindeki kinetik parametreleri tanımlamaktır. Bu nedenle, acil durumlarda veya özel popülasyonlarda kullanılan herhangi bir ilacın farmakokinetik parametreleri öğreticidir. COVID-19 bağlamında, kullanılan ilaçların farmakokinetiğini anlamak, optimum terapötik sonuçlara ulaşmak için çok önemlidir. Bu bilgi, COVID-19 hastaları için uygun dozajın, uygulama sıklığının ve tedavi süresinin belirlenmesine yardımcı olur. Farmakokinetik, potansiyel ilaç-ilaç etkileşimlerinin ve advers ilaç reaksiyonlarının olasılığının anlaşılmasında da rol oynar. Ayrıca, farmakokinetik çalışmalar COVID-19 için yeni tedavi stratejilerinin ve terapötik müdahalelerin geliştirilmesine yardımcı olabilir. Bu makalede, COVID 19 tedavisinde kullanılması önerilen favipiravir, remdesivir, lopinavir, ritonavir, klorokin ve hidroksiklorokin için temel farmakokinetik parametreler açıklanmaktadır. Bu çalışma, çeşitli COVID-19 ilaçlarının farmakokinetiği hakkında bir bilgi tabanı sağlayacaktır.

Anahtar kelimeler: COVID-19, farmakokinetik, favipiravir, remdesivir, lopinavir, ritonavir

Introduction

The COVID-19 pandemic has created an urgent need for effective therapies to treat the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While there is ongoing research and clinical trials to identify potential therapeutic targets and evaluate the efficacy of existing drugs, the results so far have been inconclusive and inconsistent. Therefore, it is crucial to understand the pharmacokinetics of drugs in COVID-19 therapy to optimize their effectiveness and minimize adverse effects. This understanding can help healthcare professionals make informed decisions about drug dosing, frequency of administration, and potential drug-drug interactions. Pharmacokinetic studies can provide valuable

information on how drugs are absorbed, distributed, metabolized, and eliminated in patients with COVID-19. These studies can also help determine the appropriate dosage adjustments for patients with altered organ function or comorbidities. In addition, the inflammatory state of COVID-19 can impact the metabolism and pharmacokinetics of drugs, especially during severe cases and cytokine storms[1].

The World Health Organization (WHO) declared the novel coronavirus disease called COVID-19 epidemic as a pandemic on March 12, 2020. As of July 4, 2021 183.5 million people have been infected with COVID-19 and the total number of people who lost their lives was 3.973 millon people[2]. The WHO was notified of an upsurge of 'pneumonia of unknown origin' observed in Wuhan City, Hubei, China on December 31, 2019. This city has a population of 11 millon residents and is a vibrant hub in central China with numerous international direct flight connections. Infected air travelers were responsible for entrance of COVID-19 outside Wuhan. Thailand reported the first international case on January 13, 2020. Rather belatedly, China's National Health Commission (NHC) announced that COVID-19 can be transmitted between humans on January 20, 2020.

The WHO designated the new coronavirus, coronavirus disease 2019, as COVID-19 on February 11, 2020[3].

Various mutant strains also have been detected which continue to complicate prevention, diagnosis, treatment and vaccination. Earlier notifications of the D614G mutation and more recent reports of variant virus strains from the United Kingdom, Denmark, and South Africa are of concern. A variant of COVID-19, which became manifest in the beginning of 2020 with a D614G mutation, replaced the initial COVID-19 strain first identified in China became the dominant form globally by June,2020. These variants, designated as variants of concern, have raised concerns due to their potential impact on transmissibility, disease severity, and the effectiveness of public health measures, vaccines, and therapeutics. The emergence of the D614G variant in early 2020 marked a significant shift in the genetic makeup of the SARS-CoV-2 virus and raised concerns among researchers, public health officials, and the general population. This variant was found to have increased transmissibility as well as potential implications for the efficacy of mitigation measures, available vaccines, and treatments. However, it is important to note that the D614G mutation alone has not been shown to cause higher mortality or alter the efficiency of current laboratory diagnostics, therapeutics, vaccines, or public health prevention strategies[4].

For many years since as early as 1963 coronaviruses affecting human beings caused mild cold symptoms. But two β- coronaviruses, genetically related to SAR-Co-2 namely severe acute respiratory coronavirus (SARS-CoV) and middle east respiratory coronavirus (MERS-CoV) caused outbreaks in 2003 and 2014 respectively[5]. Their mortality rates were 9.4 and 34.4% respectively. COVID-19, in comparison, shows lower fatalty rates ranging from 0.1 % to 8% (JHU) depending on the age of the patient infected with COVID-19. Nevertheless the immense spreading capacity causing high human-to-human transmission rate demonstrates the astonishing death toll of the pandemic. COVID-19 is the first coronavirus leading to a severe pandemic which can be ascribed to its high reproduction number (RO) [6]. The RO of COVID-19 is 3.77. This number is much higher than either that of SARS and MERS. The incubation period lasts about 5 to 8, sometimes 14, days. Around 80 % of those infected have asymptomatic disease and about 10% have mild symptoms such as cough malaise, muscular and skeletal pain, anosmia and ageusia. Around 5-15% develop acute respiratory distress syndrome (ARDS) characterized by difficulty in breathing due to pulmonary alveolar, involvement. Children, like the situation in SARS and MERS infections, are rather unlikely to be infected and likely to have milder disease[6].

The angiotensin-converting enzyme 2 (ACE2) receptor is bound by the spike (S) protein of the SARS-CoV-2 envelop. The receptor binding domain is one of the two subunits that make up this S protein. Following binding, the virus undergoes membrane fusion and is taken in by the host cell by endocytosis. While ACE2 is present in many types of cells, it is mostly found in the kidneys, small intestine, endothelium lining, and alveolar epithelial cells of the lungs. The majority of clinical manifestations, including significant lung congestion and substantial alveolar damage that results in respiratory distress, which is typically observed in severe instances, are explained by this distribution preponderance. Uncontrolled inflammation is the root cause of acute respiratory distress syndrome (ARDS), and it can occasionally trigger a powerful

immunological reaction known as a "cytokine storm." Cytokine storm necessitates another set of therapeutic measures which usually takes place in the intensive care unit including use of respiratory assistance - sometimes mechanical- and use of corticosteroides in order to counteract the massive and destructive immune response created in the patient[6]. Moreover systemic vasculitis, thrombi formation and renal failure can be partially attributed to the abovementioned receptor predominance. COVID infection may lead to myocardial damage in severe cases which sometimes also can cause neurological manifestations[5].

Since there are no specific antiviral drugs for use against COVID-19 a series of repurposing of preexisting drugs had to be carried out in order to fight the pandemic. This process included a re-research of existing antiviral agents already approved for other diseases like SARS and MERS as a compassionate use to treat COVID 19. There are several components to the treatment of COVID-19. The first part is the antiviral treatment. The second is the treatment against the immune response which usally destructs the host. Some antivirals, convalescent plasma therapies and corticosteroids are among the drug therapies explored. There have been promising treatments which were scientifically tested by worldwide trials. Some of these trials have been the WHO Solidarity Trial and The Recovery Trial. Remdesivir, lopinavir/ritonavir, interferon β_3 hydroxychloroquine and dexametasone are some of the agents studied[6]. These trials aim to assess the efficacy and safety of these agents in treating COVID-19 patients. The results from these trials will provide valuable insights into the potential use of these agents for COVID-19 treatment. The use of conventional drugs such as remdesivir, lopinavir, ritonavir, chloroquine, and hydroxychloroquine for treating COVID-19 has shown limited effectiveness.

COVID-19 Guideline of the Turkish Ministry of Health that has been revised on May 7, 2021 stipulates and permits use of only favipivavir as the sole antiviral agent for use in outpatient, inpatient and intensive care unit patients. The new algorithm does not support use of hydroxychloroquine and does not include this agent which had been in the algorthm since March 2020.

COVID-19 Treatment Guideline of NIH in the USA only permits use of remdesivir in outpatient, inpatient and intensive care unit patients. It denotes that remdesivir is the only FDA-approved drug for the antiviral treatment of COVID-19.

Favipiravir and Remdesivir

Favipiravir has been suggested by the Turkish Ministry of Health as an antiviral drug for COVID-19 therapy because to its broad-spectrum antiviral activity and its usage in nearby countries like China and Russia. Favipiravir's efficacy in treating COVID-19 remains inconclusive despite its use in clinical trials and compassionate use cases. Favipiravir's efficacy in treating COVID-19 remains inconclusive despite its use in clinical trials and compassionate use cases[7]. European Medical Agency, Natinal Health Service in the United Kingdom of Great Britain and Northern Ireland and the United States National Institute of Health (NIH) advocate the use of Remdesivir as the antiviral agent of choice. These organizations have reviewed the available data and clinical trials and believe that Remdesivir shows promise in reducing the severity and duration of COVID-19 symptoms[8]. The recommendation for Remdesivir is based on its authorization in the European Union, its approval for COVID-19 treatment in Europe, and its potential as an inhibitor of viral infection. However all of these agencies notify that these antivirals are not specific agents and are being recommended as part of a compassionate base indication because of their wide antiviral spectrum rather than specificity[9].

In 2002, favipiravir (T-705) was created as a replication inhibitor for influenza viruses[10]. On February 15, 2020, favipiravir was authorized in China for the treatment of new influenza. Additionally, Japan licensed it for the treatment of influenza[9]. It is a prodrug (T-705) with a lower molecular weight of 157.1 g/mol. Favipiravir is a type of RNA-dependent RNA-polymerase inhibitor acting as a nucleotide analog that selectively inhibits viral RNA dependent polymerase causing fatal mutagenesis when incorporated into the virus. Favipiravir also exhibits antiviral activity against arenavirus type of bunyaviruses. It has been demonstrated that as a prodrug favipiravir effectively inhibits the COVID-19 infection in VeroE6 cells[10, 11]. Adverse reactions of this antiviral agent after oral administration include increased liver function tests and testis toxicity. Favipiravir also causes an increase in blood uric acid levels. The inactive metabolite to which

favipiravir is metabolized called M1, enhances uric acid uptake via a urate transporter in the renal proximal tubules, thereby decreasing uric acid excretion into urine[9]. Favipiravir is also known for its teratogenicity. Its administration is not recommended in pregnant women[10].

Repurposing of antiviral drugs as potential antiviral treatments for COVID-19 infection led to the possible use of remdesivir for this purpose[3]. Remdesivir is a prodrug. It is a nucleoside analogue, which, based on its actions against the Ebola virus, inhibits the action of RNA-dependent RNA polymerase. Remdesivir (GS-N 5734) is a broad spectrum nucleoside (Adenine triphospate-ATP) analogue. As it is converted to nucleoside triphosphate (NTP) it inhibits transcription of viral RNA[12]. The study by the ACTT-1 Study Group Members demonstrated a 31 % faster recovery (11 days with remdesivir in comparison to 15 days with placebo) and a survival advantage of 7.1% mortality with remdesivir versus 11.9 % mortality with placebo (although statistically insignificant regarding mortality). Following the preliminary findings of the remdesivir ACTT-1 Trial conducted by the American National Institute of Allergy and Infectious Diseases (NIAID)[12–14], the Food and Drug Administration (FDA) in the United States of America (USA) issued an Emergency Use Authorization (EUA) licensing use of remdesivir for treatment of adults and children hospitalized with verified or suspected COVID-19 infection. This authorization was modified on August 28, 2020, expanding use of remdesivir to all hospitalized patients regardless of the severity of the clinical condition. On October 2020 came the regular FDA approval, becoming the only and first drug approved by FDA. The European Medical Association also authorized conditional marketing for COVID-19 treatment on June 25, 2021 (EMA January 12,2021 update).

Careful and frequent control of hepatic function and caution in patients with a creatinine clearance less than 30 ml/minute is advised when administering remdesivir[13]. This is important because hepatic function and renal clearance play a crucial role in the metabolism and elimination of drugs from the body. Monitoring hepatic function is crucial because remdesivir has been associated with elevations in hepatic enzyme levels, indicating potential liver injury. Furthermore, caution is advised in patients with impaired renal function because remdesivir has been observed to increase creatinine levels and can potentially lead to kidney damage or worsen existing renal impairment. Therefore, close monitoring of hepatic function and renal clearance parameters, such as liver enzyme levels and creatinine levels, is essential during remdesivir administration to ensure patient safety and optimize the therapeutic outcomes. This close monitoring is necessary because remdesivir metabolism can lead to drug interactions and hepatic toxicity, especially when combined with other medications commonly used in COVID-19 treatment. By carefully monitoring liver enzyme levels and creatinine levels, healthcare professionals can ensure patient safety and optimize the therapeutic outcomes of remdesivir administration. EMA advises an initial first day administration of 200 mg remdesivir follwed by 100 mg iv per day for up to 4 to 9 days as the patient's clinical condition dictates. The most ordinary side effects of remdesivir include diarrhea, rashes, hypotension. Therefore remdesivir is not a full proof weapon against COVID-19 which awaits a specific antiviral therapeutic agent [12, 13].

Lopinavir and Ritonavir

When taken in conjunction with ritonavir, lopinavir, an antiviral medication, has a longer plasma half-life due to suppression of cytochrome CYP3A4. Lopinavir is frequently used to treat HIV. It has previously been demonstrated in SARS-CoV and MERS-CoV that lopinavir aims papain-like proteases and 3C-like proteases in coronaviruses. In October 2020 the Recovery trial showed discouraging final results of lopinavir/ritonavir. The results of the Solidarity trial also were similar. This led to the announcement of WHO for an immediate termination of lopinavir/ritonavir arm of the Solidrity trial due to the absence of survival benefit[5]. The NIH also recommends against the use of lopinavir/ritonavir. The degree of oral absorption of ritonavir is high and is not affected by food. Since 20% to 40% of a 600 mg dosage of ritonavir is found in the feces as the medication remains unaltered, 60% to 80% of the dose is thought to have been absorbed. The peak plasma drug concentration (Cmax) and degree of absorption (area under the concentration-time curve (AUC)) are 23% and 7%, respectively, in liquid preparations of ritonavir when food is present. When food is present, the AUC of the ritonavir capsule formulation increases by 15%, but the Cmax remains same[15]. It is important to note that the use of lopinavir/ritonavir is still recommended as part of standard care for COVID-19 patients due to the relative safety of the combined use of these drugs

and their potential impact on viral replication. The use of lopinavir and ritonavir as combination therapy for COVID-19 has been extensively studied with initial promising results from studies during the SARS pandemic[16].

These two drugs, which are already approved for other diseases, have shown promise in inhibiting the replication of the SARS-CoV-2 virus responsible for COVID-19. However, recent clinical studies have shown mixed results regarding the effectiveness of Lopinavir and Ritonavir in treating COVID-19 symptoms and shortening the duration of viral shedding. Furthermore, there have been concerns about the adverse reactions and side effects of related antiviral drugs, such as hypocalcemia, hemolytic anemia, and liver toxicity. Despite the initial optimism surrounding Lopinavir and Ritonavir as a potential treatment for COVID-19, recent clinical studies have shown mixed results and raised concerns about their effectiveness and adverse reactions. It is necessary to conduct further research and clinical trials to determine the true efficacy and safety of Lopinavir and Ritonavir in treating COVID-19.

Chloroquine and Hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) have gained significant attention as potential treatments for COVID-19. However, it is important to note that these medications can have neurological adverse effects and can also interact with other drugs used in COVID-19 treatment. Therefore, it is crucial to carefully monitor and consider these potential risks and interactions when using chloroquine and hydroxychloroquine in COVID-19 treatment. Some experts caution against the widespread use of chloroquine and hydroxychloroquine in COVID-19 treatment without proven benefit. It is recommended that clinicians wait for the results of randomized trials before administering chloroquine and hydroxychloroquine, as there is a possibility that an ineffective and potentially harmful medication may be inappropriately administered on a large scale, potentially leading to shortages of these medications that are needed for other legitimate purposes

Currently, neither hydroxychloroquine as an antimalarial agent nor its combination (of any kind) has been approved by the US FDA or any regulatory authority worldwide. Oral absorption of these drugs is comparable to bioavailability values of 0.7-0.8. However, both drugs are known to show significant differences in bioavailability between individuals. In 40-70% of individuals who take medication, either no effect or adverse drug reactions were encountered much more frequently[17,18]. Published clinical trials generally recommend that HCQ doses start with 400 mg on the first day and continue at this dose for the next 5 days, or start with 800 mg on the first day and continue with 400 mg for the next 4 days. This last regimen also supports pharmacokinetic models that a loading dose of 400 mg oral HCQ sulfate in the morning and evening followed by a maintenance dose of 200 mg in the morning and evening for 4 days can make treatment effective and safe. This treatment protocol reached three times the potency of CQ phosphate given a total of 1000 mg / day over 5 days[19].

However randomized prospective trials, especially the WHO Solidarity trial, did not, unfortunately confirm any potential benefit of CQ in in-hospital patients and moreover reported an increase in occurence of ventricular arrythmias and prolongation of the OTC heart rate intervals resulting in decreased survival of COVID-19 patients[20, 21]. Dermatological reactions, seizures, gastrointestinal side effectsincluding vomiting and abdominal pain and hypoglycemia were also among the reported side effects. This led to US FDA's revokal of the Emergency Use Authorization of CQ on June 15, 2021.

Possible long term side effects resulting from COVID-19

COVID-19, caused by the SARS-CoV-2 virus, has not only presented as an acute respiratory illness but also as a potential long term health concern. Patients who have recovered from COVID-19 may experience persistent symptoms, impaired lung function, and various complications that affect multiple organ systems[22]. There are many possible side effects related to the long term health of individuals infected with COVID-19. They occur mainly in the cardiovascular, pulmonary and neurological systems[23]. These include cardiovascular side effects like decreased ejection fraction due to cardiomyopathy and resultant decreased expected survival[24], decreased pulmonary function due to possible micro and macro pulmonary

embolisms[25, 26]. Pulmonary embolisms may also be due to secondary pulmonary embolisms after deep vein thrombosis. Neurological sequela include palsies like occulomotor and vestibular involvement manifesting as palsies[27]. Vocal cord palsy has also been reported[28]. Psychiatric long term sequela include post-traumatic stress syndrome, anxiety[29]. These long term effects, sometimes referred to as "long COVID" or "post-acute sequelae of COVID-19," can have a significant impact on the overall health and well-being of individuals. These long-term effects of COVID-19 are still being studied and understood, but some potential side effects include:

1. Persistent fatigue and weakness: Many COVID-19 survivors report ongoing feelings of extreme tiredness and weakness, even after recovering from the acute illness. This condition, known as post-acute COVID-19 syndrome or long COVID, is characterized by a range of symptoms that can affect multiple organ systems and overall well-being
2. Respiratory complications: COVID-19 can cause long-lasting damage to the lungs, leading to persistent breathing difficulties such as shortness of breath and cough.
3. Cardiovascular issues: Some studies have shown that COVID-19 can result in cardiovascular complications, including heart inflammation, blood clots, and abnormal heart rhythms.
4. Neurological symptoms: COVID-19 has been associated with neurological effects such as headaches, dizziness, loss of taste and smell, and brain fog[30].

Discussion

COVID-19 pandemic has created a global health crisis, with a significant loss of human lives and economic impact. To combat this crisis, researchers and public health agencies are exploring the possibility of repurposing existing drugs for the potential treatment of COVID-19. Currently, there is no specific antiviral treatment available for COVID-19, and the focus of treatment is mainly on relieving symptoms. Expanding on this, clinical trials are underway to evaluate the efficacy and safety of various therapeutic agents in reducing the severity of COVID-19 and alleviating the burden on healthcare systems. These trials aim to identify drugs that can effectively counter the virus and improve clinical outcomes for patients.Additionally, it is important for clinicians to base treatment decisions on the results of well-designed randomized controlled trials, as highlighted in a systematic review of treatments used against COVID-19. Incorporated 10 completed randomized–controlled studies which brought together 1800 patients and summarized the end points of 8 studies in Table 1 and the pharmacokinetic parameters of favipiravir and remdesivir in Table 2. While multiple clinical trials are ongoing, some data have been released for remdesivir therapy. The studies gained momentum as observational studies showing a 68% improvement in the oxygen support class of seriously ill patients showed promise. A double-blind, randomized, placebo-controlled trial in which remdesivir was administered intravenously to hospitalized COVID-19 patients was published in May 2020, the Adaptive Covid-19 Treatment Trial (ACTT-1). The study of 1063 patients was a large clinical trial that demonstrated a 31% faster recovery of remdesivir. The study also found that remdesivir provided a 4% improvement in mortality compared to placebo, demonstrating a trend for survival benefit in patients treated with remdesivir. Ongoing clinical studies are investigating the difference between antiviral therapy and non-antiviral therapy[40].

Olender et al. proved an association between remdesivir treatment and critically greater improvement on the 14th day of follow-up, demonstrating the standard for COVID-19 in a study of 1130 patients. showed a 62% reduction in mortality compared to care[36].

By comparing medication plasma concentrations with concentrations predicted by the model prior to the trial, Nguyen et al. reported favipiravir concentrations discovered in patients of the JIKI trial. Analysis was done on the potential correlation between viral loads and biochemical/hematological markers[33].

Sağlam et al. obtained the favipiravir generic product license approval, which is needed during the pandemic, was carried out on healthy volunteers during the pandemic and also pharmacokinetic properties of favipiravir were evaluated[39]. The Cmax of favipiravir is linear in the dose range from 30 to 1600 mg, while

the AUC values at the dose of ≥800 mg remained higher than the value expected from the dose-proportional relationship. There were no considerable differences in tmax of favipiravir among the doses, but t1/2 and MRT prolonged at the high doses of ≥800 mg. The pharmacokinetic (PK) results of FPV in healthy individuals and a small number of influenza sufferers are covered in this study. The PKs of FPV in critically sick patients who are hospitalized to intensive care units and need invasive oxygenation, however, are not well understood. Due to increased cardiac output, capillary leak, hepatic and renal clearance, and altered protein binding characteristics, PKs are significantly altered in ICU patients. Numerous studies show that sedatives, opioids, and medications that lower gastrointestinal motility that are also used by patients in critical care have increased drug distribution volume, higher clearance, and decreased gastrointestinal absorption[41].

In patient groups receiving renal replacement therapy sepsis and associated acute kidney injury are frequently seen in association with multi-organ dysfunction syndrome and result in changes in various PK parameters. In addition, the high volume of fluid resuscitation often required in critically ill patients can significantly affect the Vd of several drugs. This can result in altered drug concentrations and potentially affect the efficacy and safety of pharmacotherapy. Drugs with a volume of distribution less than 1.0 L/kg and retained in the intravascular compartment are unlikely to be clinically meaningfully removed by renal replacement therapy as further complexity is added for dosing with possible extracorporeal CL.

Table 1. Characteristics of the trials

Tudy	Publication Date	Patient Group	Study Design	N	Age	Administration Dose of The Drug	Endpoint
Yeming Wang [31]	November 2020	Adult hospitalized patients	phase 2a, multi-center, open-label, dose-escalating investigation	35 (Low dose regimen N=16, high dose regimen N=19)	aged >18 years	Low-dosage FPV regimen: 600 mg (BID) per day as a maintenance dose after a 1600 mg (BID) loading dose administered on days 2–10. High-dosage FPV regimen: 800 mg (BID) of maintenance medication administered daily after a loading dose of 1800 mg (BID) on days 2–10. Oseltamivir 75 mg (BID) was also administered to the patients for ten days.	Observed favipiravir trough concentrations decreased significantly over time in both groups ($p < 0.01$), while oseltamivir concentrations were not significantly altered
Cai Qingxian[32]	March 2020	Patients with positive nasopharyngeal swab samples and less than 7 days from disease onset to registration were selected.	an uncontrolled, open-label investigation	80 FPV, N=35, LPV/RTV, N=45	Aged 16–75 years old	FPV (200 mg per tablet) was given orally. The dose was 1600 mg (BID) on Day 1 and 600 mg (BID) on Days 2–14. LPV/RTV (200 mg/50 mg per tablet) were given orally. The dose was LPV 400 mg/RTV 100 mg (BID). All participants received IFN-a1b 60 lg (30 lg per ampule) (BID) by aerosol inhalation.	Patients treated with FPV were found to have faster viral clearance and better chest CT changes compared with patients treated with LPV/RTV.

Thi Huyen Tram Nguyen[33]	February 2017	JIKI study, EVD verified by positive RTPCR, age ≥1 year, body weight ≥10 kg	dose-ranging investigation	126 PK sub-study participants (n = 66) 50 patients were involved in the JIKI experiment.	33.5 (5–78) 28.0 (2–80)	FPV, 2400 mg initial dosage, 2400 mg second dose, 1200 mg third dose, and 1200 mg dose every 12 hours from day 1 to day 9.	Median (range) Ctrough : 46.1 (2.3–106.9) µg/mL on day 2 and 25.9 (0–173.2) µg/mL on day 4
Xueting Yao[34]	November 2020	Having received a COVID-19 diagnosis	A single-center, open-label investigation	50	>18 years,	500 mg CQ phosphate (BID) for 7 days	The simulation results showed that the maximum CQ plasma concentration in this dosing regimens was in the vigilant threshold and the plasma CQ concentration appears to be lower than the reported in-vitro EC50 values
Réa-Neto Álvaro [35]	April 2021	Critically ill patients hospitalized with severe COVID-19	A randomized controlled study using open-label	105	>18 years	CQ 450 mg BID on day 1 and 450 mg once 44aily from day 2 to 5 and HCQ 400 mg BID on day 1 and 400 mg once 44aily from day 2 to 5	Because of the drugs large distribution daily incidence of renal dysfunction increased. (CQ t1/2 : 50 days and HCQ: 30 days) main safety concern with CQ/HCQ treatment is related to cardiovascular efects, (arrhythmias related to QT interval prolongation)
Olender et al [36]	July 2020	Hospitalized patients with SARS-CoV-2 confirmed infection, requiring supplemental oxygen	Open-label, randomized trial combined with a retrospective cohort study	1130	>18 years	Intervention: First day 200-mg loading dose, following 4 or 9 additional days 100 mg daily dose (plus standard care) Control: Standard-of-care treatment according to local clinical practice	
Wang et al [37]	May 2020	Hospitalized patients with confirmed SARS-CoV-2 infection	Multicenter, double-blind, placebo-controlled study conducted at random	237 (Remdesivir, 158 and plasebo 79)	>17 years old	Remdesivir: First day 200-mg loading dose, following 9 additional days 100 mg Daily dose Placebo: Placebo infusion	There was no statistically significant difference in time to clinical improvement between two groups.
Dickinson L [38]	June, 2011	Healthy volunteers	Model of population pharmacokinetics	16 (6 female, 3 Hispanic, and 2 black individuals)	>18 years old	Lopinavir-Ritonavir 400 mg-100 mg twice daily and 800 mg-200 mg once daily	

BID: Twice Daily, CQ: Chloroquine, CT: Computed Tomograph, EVD: Ebola virus disease, FPV: Favipiravir, HCQ: Hydroxychloroquine, JIKI: Study group, LPV/RTV: Lapinavir/Ritonavir, PK: Pharmacokinetic, RTPCR:Pregnancy control test

Table 2. Pharmacokinetic parameters of favipiravir and remdesivir

Study	Drug	Study design	N	Patient group	Dose	C_{max}	t_{max}	$t_{1/2}$	$AUC_{0-\infty}$
Onursal Saglam[39]	Favipiravir Test Reference	A two-period, randomized, cross-over trial using a single oral dosage	29	25.45 ± 3.86 years, adult	200 mg	5411.624 ± 2025.680 ng/mL 5002.171 ± 1231.177 ng/mL	0.50 hr 0.75 hr	1.266 ± 0.251 hr 1.319 ± 0.245 hr	9910.494 ± 2618.916 ng.hr/mL 10152.115 ± 2507.694 ng.hr/mL
Pimentel J[40]	Remdesivir Single (2 hr iv infusion) Multiple (30 min iv infusion)	Phase I randomised, blinded, placebo-controlled research including single and repeated doses	8	mean age of 44 years (range 19–55 years) adult	10 mg 30 mg 225 mg Day 1:200 mg Day 2-5:100 mg	220 (31.2) ng/mL 694 (18.6) ng/mL 4420 (16.0) ng/mL 2610 (12.7) ng/mL	2.01 (2.00-2.03) hr 2.02 (2.00-2.03) hr 1.97(1.95-1.08) hr Nd	0.66 (0.54-0.79) hr 0.81 (0.61-0.91) hr 1.05(0.96-1.21) hr 0.89(0.82-1.09) hr	230.0 (28.4) ng.hr/mL 773.9 (22.9) ng.hr/mL 5274.7(11.6) ng.hr/mL 1560(13.9) ng.hr/mL

C_{max}: Maximum plasma concentration, t_{max}: Time to reach maximum plasma concentration, $t_{1/2}$: Half life, $AUC_{0-\infty}$: Area under the plama concentration time curve

Conclusion

Although the success of public health measures in reducing and controlling infection rates varies from country to country, the concepts of quarantine, social distancing and hygiene have been and will continue to be the basis of prevention and primary health care for the foreseeable future. Effective treatment management of COVID patients in controlling the spread of infection will be an important part of meeting other challenges that may arise, such as this unexpected pandemic, along with the development of more effective vaccines and public health measures.

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Correspondence Address / Yazışma Adresi
Esra Demirtürk
Çukurova University
Faculty of Pharmacy
Department of Pharmaceutical Technology
Adana, Turkey
e- mail: edemirturk@cu.edu.tr

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