Pharmacokinetic Modeling of VV116 for Treatment of COVID-19

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Abstract: SARS-CoV-2 is still impacting global health and potentially will live with human in the near future. Therefore, effective oral medicines such as VV116 will play an important role in treating numerous patients and ending the pandemic. From this research, these simulated results can be used to guide clinical decisions to maximize therapeutic benefits of VV116 while avoiding potential toxicities. This compartmental modeling approach can be readily used for other drugs that have identical physiochemical properties in the clinical trial. However, caution should be exercised when the dose exceeds the linear PK range (up to 1200 mg in this case), where the model becomes invalid. As such, future study is needed to examine mixed-order or zero order PK where the dose-response is not linear. The importance of biomedical research has also inspired me to pursue a future career to fighting diseases with unmet medical needs.

1 INTRODUCTION

To curb SARS-CoV-2 viral infection, understanding the mechanism of viral infection to carry out better interventions is fundamentally important to treat patients (Shang et al., 2020). When SARS-CoV-2 binds to the surface of the host cell, its spike glycoprotein attaches to angiotensin-converting enzyme 2 (ACE2) - an entry activator (Shang et al., 2020) on the cell membrane (Unnoh et al., 2022). Upon binding to ACE2, the virus enters the cytoplasm via cell membrane with the assistance of transmembrane protease, serine 2 (Shang et al., 2020). Alternatively, COVID-19 is able to enter cells by engulfing of cell membrane directly into the cell cytoplasm (Granet, 2020). Upon the entry into the cytoplasm, the virus releases the RNA genome upon disassembly. A protein viral transcriptase complex, including RNA-dependent RNA polymerase (RdRp) and a helicase of the virus, are translated by host cellular machinery from the viral RNA of two large open reading frames(ORFs) 1ab (Zhou et al., 2020). During replication, a full-length negative-strand RNA is synthesized. Sequentially, in viral RNA translation, the RNA genome is translated into viral polyproteins, which gets cleaved by main protease (Mpro). Consequently, viral RNA and the cleaved functional viral proteins assemble into new virions and bud off from the infected cells to reach other healthy cells.

VV116 is an ester prodrug of the remdesivir parent nucleoside. Upon oral administration, VV116 is rapidly metabolized to form the parent nucleoside in the body and has thus shown great promise for the development of an oral drug for treating COVID-19 (Zhang et al., 2022). From the previous research. The viral replication is dependent on the formation of functional enzymes by cleavage of polyproteins, carried out by Mpro, which is the main target of the lead drugs, nirmatrelvir and ensitrelvir (Luttens et al., 2022). First, after oral (PO) administration, VV116 gets absorbed in the gastrointestinal (GI) tract and enters systemic circulation. It then distributes into cells owing to the lipophilicity of the ester pro-moiety. Upon entering the cell, VV116 gets hydrolyzed to form the parent nucleoside (GS-441524 analog). Then the nucleoside gets phosphorylated by kinases inside the cells to form triphosphate (TP), which binds to RdRp to inhibit viral replication. The major reason that accounts for its short circulation is quick elimination by cytochrome P450 (CYP) enzymes, specifically CYP3A4 (Owen et al., 2021).

This research project aims to build a pharmacokinetic model for VV116 based on phase 1 and 2 clinical trials, which could help predict the optimal dosing regimen for better clinical outcomes.

2 METHOD

2.1.Selecting a Template

To achieve this research objective, the first step is to understand the pharmacokinetic profile of VV116 in healthy volunteers. This is based on compartmental pharmacokinetics (PK) modeling using non-linear regression. PK is used to determine changes in drugs in the body to identify properties of drugs. In order to simulate the PK, we identified four critical components involved in the process, including absorption, distribution, metabolism, and excretion, namely ADME. Absorption is a process by which a drug enters the systemic circulation...
from the administration site. The main pathways of absorption include oral absorption, dermal absorption, topical absorption, and subcutaneous absorption. IV administration is not subjective to absorption process. Absorption has a rate (amount of drug absorbed per unit time) and an extent (total amount of drug). Absorption processes are key to the generic drug industry. Distribution is a process by which a drug moves from the systemic circulation to peripheral tissues throughout the body. Distribution is affected by the PK parameters, but it is very difficult to quantify distribution with a PK parameter. Metabolism is defined as the chemical or enzymatic transformation of the parent drug into metabolite form. Metabolites is usually more polar which promotes urinal excretion. The primary organ that governs metabolism is liver, which is abundant in cytochrome P450 family of enzymes, the main enzymatic system responsible for metabolism.

Because PK essentially dictates the circulation of drugs within blood vessels, it lays the foundation for determining the route of administration, dose, and dosing interval. PK can be described by PK parameters using Equation 1. In simple terms, it is a study of what the body does to the drug and the information can be obtained using the time course of drugs measured in plasma. In this research project, determining VV116 PK parameters in humans can help decide the amount of dose and dosing frequency. These PK parameters can be derived from compartmental analysis of oral single ascending dose in healthy volunteers reported in phase 1 clinical trial.

Equation 1. Pharmacokinetic equation for one-compartmental model.

\[
C(t) = \frac{F \times D}{V} \times \frac{k_a}{(k_a - k_e)} \times \left( e^{-\frac{k_e}{V} t} - e^{-\frac{k_a}{V} t} \right)
\] (1)

As a first step, the area under the curve (AUC) can be obtained using plasma concentration versus time plot (PK curve), shown in Figure 2. This PK curve was used to determine initial estimates using non-compartmental analysis (NCA). Calculation of these initial estimates was accomplished using formulated Excel spreadsheet. These initial estimates were then used to derive more accurate PK parameters using compartmental modeling with Phoenix 64 8.3.4.295. Based on the compartmental model, simulation was performed using different doses of VV16 at 25, 200, 400, 800, and 1200 mg dose levels every 24 hours (QD) and every 12 hours (BID). The therapeutic window is defined by minimum effective concentration at EC50 and highest tolerable concentration at 5% CC50 based on the literature report. The therapeutic window is a critical component of an optimal dosing regimen (Qian et al., 2022).

![Figure 1](image1.png)

**Figure 1** VV116 plasma concentration over time upon oral administration at 25, 200, 400, 800, and 1200 mg, digitized from the published clinical trial

The utility of the PK equation is to describe the plasma concentration of drugs at any time after the dose. To calculate this plasma concentration, several important PK parameters have to be determined, including F, D, V, \( k_a \), \( k \), CL, Ke and \( t/2 \). The definition of these PK parameters is as follows (Murphy, 2011): bioavailability (F) refers to the fraction of administered drug that actually enters systemic circulation.

Dose (D) is the amount of dose administered. In this study, a single ascending dose of 25, 200, 400, 800, and 1200 mg was administered to five groups of healthy volunteers.

Volume of distribution (V) is the proportionality factor between the amount of drug in the body and the concentration in the plasma.

Absorption rate constant (\( k_a \)) is the rate at which a drug enters the systemic circulation from the site of administration. It is expressed per unit of time. \( k_a \) is related to the absorption half-life (\( t/2a \)) per the following equation: \( k_a = \ln(2) / t1/2a \). For oral administration, the absorption process occurs in the gastrointestinal tract.

Clearance (CL) is a measure of the ability of the body to remove a drug from the body, defined as per volume cleared from the body per unit time. It is a proportionality factor that relates the actual concentration in the body to the rate of elimination. When exposure increases linearly with dose, clearance is constant, which is also referred to as linear PK; as a result, the rate of drug elimination (mg/hr) is proportional to drug concentration in plasma.

Elimination rate constant (\( k_e \)) describes the rate at which a drug gets removed from the systemic circulation.

Half-life (\( t1/2 \)) is half-life which is the time required for the concentration to decrease by \( 1/2 \) of the original
value. Oftentimes, the drug is considered to be completely removed from the body after five half-lives.

There are generally two approaches to obtaining these parameters: Non-compartmental analysis (NCA) and compartmental modeling. NCA is a well-established model in the field of pharmacokinetic analysis. NCA is model-independent, and therefore it does not rely on models of the organ or tissue systems but rather is built upon algebraic equations to estimate pharmacokinetic parameters. It should be noted that NCA can only be used in retrospective analysis, and not for prospective simulation or prediction. On the other hand, the compartmental analysis considers the body to consist of kinetically homogeneous and well-mixed compartments. The number of compartments is driven by the number of different kinetic processes observed in the concentration-time profile. Owing to the mathematical method used, i.e., nonlinear regression, compartmental modeling is sometimes referred to as non-linear PK analysis. It is worth noting that compartmental modeling is more computation-intensive and relies on initial estimates of some important PK parameters; however, unlike NCA, compartmental modeling can be used in a prospective manner to predict the PK profile of a drug under different dosing regimens (Team, 2018). In this research project, NCA was performed using Excel built-in with PK equations to obtain initial estimates for CL and V. These initial estimates were then used for non-linear PK modeling using the extravascular one-compartmental model.

A typical one-compartmental model is shown in Figure 3. The total amount of drug administered is contained in an absorption compartment, noted as Aa. A fraction of this amount (A1) enters the central compartment (C) at an absorption rate constant Ka. This central compartment is also the site of measurement where the drug concentration (Cobs) can be obtained. To relate this concentration in central compartment with the amount absorbed, the volume of distribution (V) can be calculated using A1/Cobs. However, since A1 cannot be determined as only oral administration was given; therefore, V is expressed as Aa*F/Cobs, where F is the oral bioavailability of the drug. The drug gets removed from the central compartment at a rate determined by clearance (CL). Finally, the amount of drug absorbed must equal the amount eliminated (A0), according to mass balance.

Figure 2 Extravascular one-compartmental model used in this analysis. Aa: administered dose; Ka: absorption rate constant; C: central compartment; V: volume of distribution; A1: amount enters systemic circulation; CL: clearance; A0: amount eliminated; Cobs: measured plasma concentration.

3 RESULTS AND DISCUSSION

The results obtained that Ka was found to range from 0.69 to 4.42 /hr, highest in 25 mg, which decreases with the increase in dose. This suggests that absorption was likely reaching saturation with higher doses. Similarly, the V highest value was found in 1200 mg, with a range between 167,556 and 413,168 mL, which suggests that the volume increases with an increase in dose. CL was found to range from 26030 to 42040 mL/hr, highest in 1200mg, which roughly increases with increase of dose. Ke was found to range from 0.16 to 0.110 1/hr, highest in 25 mg, which decreases with the increase in dose. This indicates that elimination was likely reaching saturation at a higher dose. t1/2 was found to range from 4.46 from 6.81 hr, highest in 1200 mg, with longest half-life in 800 mg dose group. Therefore, this difference in t1/2 is likely due to individual variability. This elucidates that the lasting of drug efficacy increases. With the foregoing PK parameters determined through compartmental modeling, simulation was carried out to predict the PK profile for different dose regimens.

The simulated plasma concentration-time plots are shown in Figures 3-7. The solid blue and orange lines represent QD and BID dosing, respectively. For the therapeutic window, the half maximal effective concentration (EC50, grey dotted line) was set as the minimum effective concentration; whereas the maximum tolerated concentration was determined by 5% half-maximal cytotoxic concentration (CC50, yellow dotted line). Concentration below EC50 would be considered not therapeutically effective, while greater than 5% CC50 would be considered to cause potential toxicity.
As shown in Figure 3, both 25 mg QD and BID were below EC50, which indicates they cannot reach effective concentration in patients. Therefore, this dosing regimen underdelivers the drug and should generally be avoided.

Figure 4 Simulated 7-day plasma PK curve upon 200 mg oral administration of VV116.

200 mg regimens are shown in Figure 5. The BID PK curve was above EC50 half of the time; in comparison, the QD PK curve was above EC50 only 20% of the time. However, neither of them reached the upper limit to cause toxicity concerns. These results suggest that a 200 mg dose of VV116 is less optimal for patients.

Figure 5 Simulated 7-day plasma PK curve upon 400 mg oral administration of VV116.

As suggested in Figure 6, 400 mg BID appears to be the optimal dosing regimen because the PK curve was above EC50 at all times, while not exceeding the upper limit of 5% CC50. In contrast, 400 mg QD was only above EC50 half of the time. It should be noted that at Cmax, BID was a marginally above 5% CC50, which should not cause significant concern for toxicity. This is because 5% CC50 is a conservative upper limit for safety, transiently reaching this limit is unlikely to cause safety concerns.

Figure 6 Simulated 7-day plasma PK curve upon 800 mg oral administration of VV116.
800 mg PK curves are shown in Figure 7. Notably, for BID dosing, Cmax was 40% above the upper limit of 5% CC50, which might lead to safety concerns. In comparison, 800 QD did not significantly exceed this upper limit. Although, the QD dose was below EC50 30% of the time below, it is more convenient than BID regimen, which can help improve patient adherence. These results demonstrate that 800 mg QD is relatively effective and safe as a more convenient dosing regimen.

Figure 7 Simulated 7-day plasma PK curve upon 1,200 mg oral administration of VV116.

Finally, the predicted PK curve for the highest dose group 1200 mg QD and BID are shown in Figure 8. As expected both are well above EC50; however, both significantly exceeded the upper limit of 5% CC50, with BID reaching 200% of the safety threshold. These results indicate that 1200mg QD and 1200mg BID although exhibit considerable efficacy, they carry a significant risk of being toxic to patients.

As indicated in the simulated results, based on this therapeutic window, 400 mg BID was predicted to be the best dosing regimen that balances efficacy and toxicity. Moreover, 800 mg QD is a more convenient choice for patients as once daily dose, despite the plasma concentration falling below EC50 30% of the time.

4 CONCLUSION

SARS-CoV-2 is still impacting global health and potentially will live with human in the near future. Therefore, effective oral medicines such as VV116 will play an important role in treating numerous patients and ending the pandemic. From this research, these simulated results can be used to guide clinical decisions to maximize therapeutic benefits of VV116 while avoiding potential toxicities. This compartmental modeling approach can be readily used for other drugs that have identical physicochemical properties in the clinical trial. However, caution should be exercised when the dose exceeds the linear PK range (up to 1200 mg in this case), where the model becomes invalid. As such, future study is needed to examine mixed-order or zero order PK where the dose-response is not linear. The importance of biomedical research has also inspired me to pursue a future career to fighting diseases with unmet medical needs.

REFERENCES


