Model based characterization of pharmacokinetic interaction between voriconazole and cytarabine in patients with acute myeloid leukemia

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Abstract

Voriconazole is a broad spectrum antifungal agent. Patients with acute myeloid leukemia that are susceptible to fungal infections receive simultaneously voriconazole and antitumor regimens. Drug-drug interactions between voriconazole and cytarabine involving the CYP3A4 enzyme are thought to affect the pharmacokinetic profile of the drugs and as a result their toxicological or pharmacological outcome. Population pharmacokinetic models were used to characterize these interactions and optimize the dose schemes after coadministration. Simulations and estimations were conducted by using NONMEM. The optimal dose for one hour intravenous infusion of voriconazole was estimated to 5mg/h. The proposed time points based on the pharmacokinetic profile of voriconazole for validated the model by using a small cohort of patients are 2h, 26h, 27h, 50h, 51h, 120h, 335h, 336h after the first administration of the antifungal agent.
Περίληψη

Η βορικοναζόλη αποτελεί έναν ευρέως φάσματος αντιμυκητιασικό παράγοντα. Ασθενείς με οξεία μυελογενή λευχαιμία (ΟΜΛ) που θεωρούνται ευπαθείς στην ανάπτυξη μυκητιάσεων λαμβάνουν βορικοναζόλη σε συγχορήγηση με τα αντικαρκινικά φάρμακα. Αλληλεπιδράσεις φαρμάκων που λαμβάνουν χώρα κατά την διάρκεια του μεταβολισμού των χρησιμοποιούμενων φαρμάκων από κοινά ισοένζυμα του κυττοχρώματος P450 πιθανότατα να επηρεάζουν το φαρμακοκινητικό προφίλ τών φαρμάκων. Πληθυσμιακά φαρμακοκινητικά μοντέλα χρησιμοποιήθηκαν για τον χαρακτηρισμό αυτών των αλληλεπιδράσεων και την βελτιστοποίηση του δοσολογικού σχήματος. Προσομοιώσεις και υπολογισμοί πραγματοποιήθηκαν μέσω του προγράμματος NONMEM. Η βέλτιστη δόση μετά μια ώρα έγχυσης της βορικοναζόλης είναι 5mg/L. Τα προτεινόμενα χρονικά σημεία βασισμένα στο φαρμακοκινητικό προφίλ της βορικοναζόλης για την διεξάγωση μικρού μήκους κλινικής μελέτης που θα επιτρέψει την αξιολόγηση του μοντέλου είναι 2h, 26h, 27h, 50h, 51h, 120h, 335h, 336h μετά την χορήγηση του αντιμυκητιασικού φαρμάκου.
Acknowledgements

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Introduction

Part I
1. Acute myeloid leukemia

1.1 General background

All blood cells are descended from a single population of bone marrow cells called pluripotent hematopoietic stem cells, which are undifferentiated cells capable of giving rise to precursors of any of the different blood cells. When a pluripotent stem cell divides, its two daughter cells either remain pluripotent stem cells or become committed to a particular developmental pathway. The first branching yields either lymphoid stem cells, which give rise to the lymphocytes or so-called myeloid stem cells, the progenitors of all the other varieties. At some point, the proliferating offspring of the myeloid stem cells become committed to differentiate along only one path (figure 1)\(^1\).

Proliferation and differentiation of various progenitor cells is stimulated, at multiple points, by a large number of protein hormones and paracrine agents collectively termed hematopoietic growth factors (HGFs)\(^1\).

Figure 1: Production of blood cells by the bone marrow
Cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream is defined as leukemia. Clinically and pathologically, leukemia is subdivided into a variety of large groups. The first division is between its acute and chronic forms. Additionally, the diseases are subdivided according to which of blood cell is affected. This split divides leukemias into lymphoblastic or lymphocytic leukemia and myeloid or myelogenous leukemia\(^2\).

Acute myeloid leukemia (AML) is one of the most common types of leukemia among adults. It is characterized by infiltration of the blood, bone marrow, and other tissues by neoplastic cells of the hematopoietic system. The incidence of AML is ~3.5 per 100,000 per year. Moreover the incidence is increased with the age and it is higher in men than in women. According to the World Health Organization (WHO) acute myeloid leukemia is classified into eight different biologically distinct groups based on clinical and cytogenetic and molecular abnormalities in addition to morphology (table 1)\(^2\).

**Table 1: Classification of acute myeloid leukemia**

<table>
<thead>
<tr>
<th>AML Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML with recurrent genetic abnormalities</td>
</tr>
<tr>
<td>AML with myelodysplasia-related changes</td>
</tr>
<tr>
<td>Therapy-related myeloid neoplasms</td>
</tr>
<tr>
<td>AML not otherwise specified</td>
</tr>
<tr>
<td>Myeloid sarcoma</td>
</tr>
<tr>
<td>Myeloid proliferations related to Down Syndrome</td>
</tr>
<tr>
<td>Blastic plasmacytoid dendritic cell neoplasm</td>
</tr>
<tr>
<td>Acute leukemia of ambiguous lineage</td>
</tr>
</tbody>
</table>

Furthermore AML can be classified according to genetic (chromosomal and molecular) findings. Chromosomal analysis of the leukemic cell provides the most important pretreatment prognostic information in AML. The classification after the incorporation of cytogenetics according to WHO is a) AML with recurrent genetic abnormalities and b) AML
with myelodysplasia related changes. Molecular study of many recurring cytogenetetic abnormalities has revealed genes that may be involved in leukomogenesis. This information can be used to further classification of AML. However further reference to AML classification is beyond the purpose of the project\textsuperscript{[2]}. 

Patients with AML most often present with nonspecific symptoms that begin gradually or abruptly and the consequence of anemia, leukocytosis, leukopenia or leukocyte dysfunction, or thrombocytopenia. In addition most complain of fatigue or weakness at the time of diagnosis. Anorexia, weight loss, abnormal hemostasis, bone pain, lymphadenopathy, nonspecific cough, headache are symptoms that maybe present\textsuperscript{[3]}. 

Regarding the hematologic findings anemia is usually present and can be severe. Furthermore in comparison with the median presenting leukocyte count which is 15.000/\mu L between 25 and 40\% of patients have counts < 5000/ \mu L and 20\% have counts >100.000/ \mu L. Fewer than 5\% have no detectable leukemic cells in the blood\textsuperscript{[3]}. 

\textbf{1.2 Treatment} 

There are different types of treatment for patients with acute myeloid leukemia. Some treatments are standard, and some are being tested in clinical trials. The four types of standard treatment are used are: a) chemotherapy b) radiation therapy b) Stem cell transplant and c) other drug therapies\textsuperscript{[2]}. 

The mainstay of the therapeutic approach of acute myeloid leukemia is systemically administered combination chemotherapy. Future approaches involving risk-group stratification and biologically targeted therapies are being tested to improve antileukemic treatment while sparing normal tissues. Optimal treatment of acute myeloid leukemia requires control of bone marrow and systemic disease\textsuperscript{[2]}. 

Treatment is ordinarily divided into two phases: (1) induction (to attain remission), and (2) postremission consolidation/intensification. Postremission therapy may consist of
varying numbers of courses of intensive chemotherapy and/or allogeneic hematopoietic stem cell transplantation\textsuperscript{3}.

During the induction chemotherapy cytarabine is administrated as continuous intravenous infusion for seven days in conjunction with anthracycline (daunorubicin or idarubicin) for three days. Up to 70\% of patients will achieve a remission with this protocol. Other alternative induction regimens, including high-dose cytarabine alone or investigational agents may also be used\textsuperscript{3}.

Consolidation therapy is used to distinguish the small amount of likely non detectable leukemic cells with the current diagnostic techniques. Patients receive cytarabine and idarubicin or daunorubicin in doses similar to those given initially (table 2), but for five and two days, respectively. The therapeutic protocol comprises six cycles in a period of five weeks\textsuperscript{3}.

Unfortunately for patients with relapsed AML the treatment options are limited. Monoclonal antibodies, cytotoxic drugs and other targeted therapies are under investigation. Ultimately palliative care may be offered\textsuperscript{3}.

**Table 2:** Doses of anticancer regiments

<table>
<thead>
<tr>
<th>Anticancer regimen</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine</td>
<td>100-200mg/m\textsuperscript{2}</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>12mg/m\textsuperscript{2}/day</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>60-90mg/m\textsuperscript{2}/day</td>
</tr>
</tbody>
</table>
1.3 Antifungal therapy in patients with AML

Invasive fungal infections remain an important cause of morbidity and mortality in patients with acute myeloid leukemia. Advances in the pharmacotherapy of fungal infections and a shift in the epidemiological characteristics of fungal pathogens toward fluconazole-resistant Candida species and saprophytic molds have place a greater emphasis on selection of broader-spectrum agents for empirical therapy of invasive fungal infections in the high risk population\textsuperscript{[4-5]}. 

Since the 1990s, there has been acceleration in introduction of new antifungal agents to the clinic. These agents have a broader spectrum of antifungal coverage (table 3) and improved tolerability, compared with the amphotericin B-based regiments. Other regimens that are used for the same purpose are called echinocandins. These agents used prophylactically, empirically and preemptively or for documented invasive fungal infections in leukemia patients\textsuperscript{[5-7]}.

Regarding the antifungal prophylaxis strategy not all patients with acute myeloid leukemia are at the same risk of invasive fungal infections. High risk patients susceptible to fungal infections (i.e. older patients) should receive antifungal prophylaxis. However there are no guidelines that indicate the dose scheme of the antifungal agents during prophylaxis\textsuperscript{[7-8]}.
Table 3: In vitro activity of currently used antifungal agents.
– no activity, +/- moderate activity, +activity

<table>
<thead>
<tr>
<th>Fungal species</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>posaconazole</th>
<th>voriconazole</th>
<th>Amphotericin</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus fumigatus</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aspergillus flavus</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aspergillus terreus</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other candida species</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Coccioidiodes species</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Fusarium species</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Scedosporium apiospermum</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Sceosporium prolificans</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trichosporon</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

Despite increasing focus on preemptive treatment approaches, empirical antifungal therapy is still an accepted practice, supported by the suboptimal early diagnosis of invasive fungal infections and the crucial role of early initiation of antifungal therapy. In an era in which persistent fever in neutropenic patients has an increasingly complex differential diagnosis, it is important that antifungals are not prescribed without careful clinical evaluation. Typically antifungals are empirically administered after 3-7 days of persistent fever with neutropenia in patients who are receiving broad-spectrum antibiotic. The following table summarizes the dose schemes of the most used antifungal agents in clinical practice[8-9].
Table 4: Dose schemes of most used antifungal agents in clinical practice

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
<th>Amphotericin</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12mg/kg/day</td>
<td>200mg twice a day</td>
<td>800mg/day in 4 divided doses</td>
<td>6mg/kg twice a day on day 1, then 4mg/kg twice a day</td>
<td>0.5-1 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>for the first 2 days</td>
<td>for the first 7 days and then in 2 divided doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and then 200mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It is well known that antifungal therapy implies risk. According to the good clinical practice these risk should be minimized. Drop outs of patients due to toxicity or the sub therapeutic effects of the agents have been reported. There are different factors influencing decision making of antifungal therapy in leukemia patients which are representing bellow:

1. Risk of nephrotoxicity (higher patient age, concomitant nephrotoxic drugs, or renal impairment)
2. Liver dysfunction
3. Ability for oral medication—gastrointestinal function (mucositis, nausea, and vomiting)
4. Active leukemia and plans for hemopoietic transplant
5. Type of chemotherapy (remission induction vs consolidation vs palliation)
6. Type of fungus
7. Site of infection (eg, central nervous system disease)
8. Certainty of diagnosis
9. Interactions of concomitant drugs with antifungals
10. Infected hardware or catheters
11. Prior antifungal exposure (risk of cross-resistance or tolerance with azoles)
12. Refractory IFI and number of previously failed regimens
13. Patient’s preference and ability to pay for oral antifungals
14. Immunosuppression and reconstitution (timing and intensity of immunosuppression)
15. Concomitant infections (cytomegalovirus or bacteria) and their treatment
16. Patient’s compliance
17. Outpatient vs inpatient treatment
In conclusion, tremendous progress has been made in the treatment of invasive fungal infections in acute myeloid leukemia patients over the last decades. However more work should be done on optimizing the prophylactic antifungal treatment and guidelines should be written.
2. Pharmacokinetic principles

2.1 Introduction

Pharmacokinetics is the study of drug absorption, distribution, metabolism and excretion. These pharmacokinetic processes often referred to as ADME, determine the drug concentration in the body when medicines are prescribed. A fundamental understanding of these parameters is required to design an appropriate drug regimen for patient. The effectiveness of a dosage regimen is determined by the concentration of the drug in the body\textsuperscript{[12-13]}.

Ideally, the concentration of drug should be measured at the site of action of the drug; that is, at the receptor. However, owing to inaccessibility, drug concentrations are normally measured in whole blood from which serum or plasma is generated. Other body fluids such as saliva, urine and cerebrospinal fluid (CSF) are sometimes used. It is assumed that drug concentrations in these fluids are in equilibrium with the drug concentration at the receptor\textsuperscript{[12-13]}.

It should be noted that the measured drug concentrations in plasma or serum are often referred to as drug levels, which is the term that will be used throughout the text. It refers to total drug concentration, i.e. a combination of bound and free drug that are in equilibrium with each other\textsuperscript{[12-13]}.

In routine clinical practice, serum drug level monitoring and optimization of a dosage regimen require the application of clinical pharmacokinetics. A number of drugs show a narrow therapeutic range and for these drugs therapeutic drug level monitoring is required\textsuperscript{[12-13]}.

A variety of techniques is available for representing the pharmacokinetics of a drug. The most usual is to view the body as consisting of compartments between which drug moves and from which elimination occurs. The transfer of drug between these compartments is represented by rate constants\textsuperscript{[12-13]}. 
To consider the processes of ADME the *rates* of these processes have to be considered, they can be characterized by two basic underlying concepts. The rate of a reaction or process is defined as the velocity at which it proceeds and can be described as either zero-order or first-order\textsuperscript{[12-13]}

2.3 Pharmacokinetic parameters

2.3.1 Volume of distribution

The volume of distribution (Vd) has no direct physiological meaning; it is not a ‘real’ volume and is usually referred to as the apparent volume of distribution. It is defined as that volume of plasma in which the total amount of drug in the body would be required to be dissolved in order to reflect the drug concentration attained in plasma\textsuperscript{[12-13]}.

2.3.2 Clearance

Drug clearance (CL) is defined as the volume of plasma in the vascular compartment cleared of drug per unit time by the processes of metabolism and excretion. Clearance for a drug is constant if the drug is eliminated by first-order kinetics. Drug can be cleared by renal excretion or by metabolism or both. With respect to the kidney and liver, etc., clearances are additive that is: $\text{CL}_{\text{total}}=\text{CL}_{\text{renal}}+\text{CL}_{\text{nonrenal}}$\textsuperscript{[12-13]}

2.3.3 Half-life

The time required to reduce the plasma concentration to one half its initial value is defined as the half-life ($t_{1/2}$). This parameter is very useful for estimating how long it will take for levels to be reduced by half the original concentration. It can be used to estimate for how
long a drug should be stopped if a patient has toxic drug levels, assuming the drug shows linear one-compartment pharmacokinetics\(^{12-13}\).

### 2.3.4 Elimination rate constant

The elimination rate constant ($k_{el}$) is the first order rate constant describing drug elimination from the body. This is an overall elimination rate constant describing removal of the drug by all elimination processes including excretion and metabolism. Metabolites are different chemical entities and have their own elimination rate constant. The elimination rate constant is the proportionality constant relating the rate of change drug concentration and concentration or the rate of elimination of the drug and the amount of drug remaining to be eliminated\(^{12-13}\).

### 2.3.5 Bioavailability

Bioavailability ($F$) is a subcategory of absorption and is the fraction of an administered dose of unchanged drug that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered intravenously, its bioavailability is 100%. However, when a medication is administered via other routes (such as orally), its bioavailability generally decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient\(^{12-13}\).

### 2.2 Pharmacokinetic compartmental models

Pharmacokinetic models are hypothetical structures that are used to describe the fate of a drug in a biological system following its administration. These models can be characterized as one compartmental, two compartmental or multi compartmental models.
Regarding the one-compartment model, following drug administration, the body is depicted as kinetically homogeneous unit. This assumes that the drug achieves instantaneous distribution throughout the body and that the drug equilibrates instantaneously between tissues. Thus the drug concentration-time profile shows monophasic response\textsuperscript{[12-13]}. 

![Diagram of one-compartment model](image)

**Figure 2:** One compartment-model.

It is important to note that this does not imply that the drug concentration in plasma is equal to the drug concentration in the tissues. However, changes in the plasma concentration quantitatively reflect changes in the tissues. The relationship can be blotted on a log Cp vs time graph and will then show a linear relation\textsuperscript{[12-13]}. 

20 | Page
Figure 3: Plasma concentration versus time profile to normal and log normal scale respectively of a drug showing a one-compartment model.

The two-compartment model resolves the body into a central compartment and a peripheral compartment. Although these compartments have no physiological or anatomical meaning, it is assumed that the central compartment comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin\textsuperscript{12-13}.

A two-compartment model assumes that, following drug administration into the central compartment, the drug distributes between that compartment and the peripheral compartment. However, the drug does not achieve instantaneous distribution i.e. equilibration between the two compartments\textsuperscript{12-13}. 
Figure 4: Two compartment-model.

The drug concentration-time profile shows a curve but the log drug concentration-time plot shows a biphasic response and can be used to distinguish whether a drug shows a one or two compartmental model\(^{[12-13]}\).

Figure 5: Plasma concentration versus time profile to normal and log normal scale respectively of a drug showing a one-compartment model.
In the multicompartment model the drug distributes into more than one compartment and the concentration-time profile shows more than one exponential. Each exponential on the concentration-time profile describes a compartment$^{12-13}$.

Figure 6: Plasma concentration versus time profile to normal and log normal scale respectively of a drug showing a three-compartment model.

2.3 Non-linear pharmacokinetics - Michaelis-Menten Kinetics

Michaelis-Menten kinetics is used whenever the elimination of a drug doesn’t follow first order Kinetics. In most cases, that means that the drug is metabolized by the microsomal enzyme system. These pharmacokinetics are often described as dose dependent pharmacokinetics with the elimination rate (equation 1) approaching a maximum rate ($V_m$). The maximum rate achieved by the system at saturating substrate concentrations. During that phenomenon the concentration of the drug is very high relative to the concentration of available enzyme molecules. The michaelis-menten constant ($K_m$)
that is included in the formula is equal to the substrate concentration at which the reaction rate is half its maximum value\[^{13}\].

\[
v = \frac{V_{\text{max}}^* [S]}{K_m + [S]} \quad (1)
\]

Based on this relationship it is worth mentioning that as the rate of the drug metabolism (v) changes as a function of drug concentration. At very low drug concentrations the available enzymes are much higher and the rate of metabolism is increased almost proportionally. However at certain concentrations the metabolic rate increases less proportionally. When the maximum concentration has been reached further increase of the drug concentration does not affect the metabolic rate\[^{13}\].

### 2.4 Drug-Drug interactions (DDIs)

A Drug-Drug interaction (DDI) is characterized by the alteration of the effect of a drug in some way, by the presence of another drug. Until recently, little emphasis had been placed on that kind of interactions. Nowadays, however clinicians take into consideration the DDIs due to the life-threatening interactions that have been observed among marketed medications\[^{15-21}\].

A DDI is classified according to the mechanism by which it occur, the resulting effect (toxicity or loss of efficacy), the clinical severity of the effect (minor, moderate, or severe) and the likelihood that the adverse outcome is due to the interaction (unlikely, possible, suspected, probable ore established). Mechanisms of drug interactions can be characterized as either pharmacodynamics (when a drug interferes with a second drug at its target site, or changes in some way its anticipated pharmacologic response) or pharmacokinetic (when...
one drug alters the absorption, distribution, metabolism or elimination of another drug, thereby changing the concentration in plasma and, consequently, at the targeted site of action.

Interactions affecting drug absorption may result in changes in the rate and extent of absorption. However, interactions that reduce the level of absorption are not typically clinically important for maintenance medications, as long as the total amount of drug absorbed is not affected. The extent to which a drug is absorbed can be affected by changes in drug transport time or gastrointestinal motility, gastrointestinal pH, intestinal cytochrome P450 (CYP) enzyme and transport protein activity, and drug chelation in the gut. In general, only 20% of the drugs that affect the extent of the drug absorption is considered clinically significant.

Theoretically, drugs that are highly protein bound may displace other highly protein-bound drugs from binding sites, thereby increasing drug distribution. In actuality, there are very few clinically relevant interactions that result from disruption of protein binding. Only for drug with a limited distribution, narrow therapeutic index, or a long elimination half-life, the increase in the abundant concentration maybe considered clinically significant.

DDIs that affect drug metabolism are related to the inhibition of induction of CYP isoenzymes. Drugs that interact due to the modulation of CYP-mediated metabolism are substrates inhibitors or inducers of the Cytochrome P450. Inhibition of the enzyme activity is a common mechanism of clinically significant metabolic drug interactions. Enzyme inhibition decreases the rate of drug metabolism, thereby increasing the amount of drug in the body, leading to accumulation and potential toxicity. The inhibition can be characterized as irreversible or reversible competitive, noncompetitive or uncompetitive (table 2). Enzyme induction may increase the intestinal and hepatic clearance of drugs, subsequently altering the serum concentration. Recently the nuclear pregnane X (PXR) and constitutive androstane receptor (CAR) were identified as inducers of CYP3A and CYP2B, respectively.

Last but not least, a variety of transport protein may be involved to different extents in drug interactions that alter the absorption, distribution metabolism and elimination of medications. Transporters such as the MDR protein, P-glycoprotein, multidrug resistance-
related proteins, organic anion transport polypeptides, organic cation transporters, and organic anion transporters may be altered by xenobiotics, thereby affecting the disposition of co-administered drugs that are transporter by proteins\textsuperscript{[15-21]}.

**Table 5: Enzyme inhibition characterization**

<table>
<thead>
<tr>
<th>ENZYME INHIBITION</th>
<th>( \text{% inhibition} = \frac{[I]/K_I}{1 + [I]/K_I + [S]/K_m} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reversible</strong> (enzymatic activity is gained by the systemic elimination of the inhibitor)</td>
<td>Competition between substrate and inhibitor for the enzyme’s active site. Competition can be overcome by increasing the concentration of substrate, thereby sustaining the enzymatic reaction despite the presence of inhibitor. The degree to which the substrate Km for the reaction is increased by inhibition depends upon the concentration of inhibitor present.</td>
</tr>
<tr>
<td><strong>Competitive</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Noncompetitive</strong></td>
<td>Competition can’t be overcome by increased substrate concentration. The inhibitor binds to a separate site of the enzyme, rendering the enzyme-substrate complex nonfunctional.</td>
</tr>
<tr>
<td><strong>Uncopentitive</strong></td>
<td>Competition results only when the inhibitor binds only to the substrate-enzyme complex.</td>
</tr>
<tr>
<td><strong>Irreversible</strong> (the intermediate forms a covalent bond with the CYP protein or its heme component, causing permanent inactivation)</td>
<td></td>
</tr>
<tr>
<td><strong>Quasi-irreversible</strong> (the intermediate is too tightly bound to the heme portion of the enzyme thus practically irreversibly bound)</td>
<td></td>
</tr>
</tbody>
</table>
3. Population pharmacokinetic modeling

3.1 Drug development and pharmacometrics

Drug development and regulatory decisions are driven by information that is compiled primarily from clinical trials and other supportive experiments, but also through clinical experience in the post-market period. The wisdom of these decisions determines the efficiency of drug development, the decision to approve the drug, and the resultant drug product quality including guidance on how to use the product known as the label. While the decisions are usually simple in nature (e.g., trial design and project progression at the company, product and labeling approval at regulatory agencies), the data informing the decision are complex and diverse\(^{[22]}\).

Pharmacometrics is an emerging science defined as the science that quantifies drug, disease and trial information to aid efficient drug development and/or regulatory decisions. Drug models describe the relationship between exposure (or pharmacokinetics), response (or pharmacodynamics) for both desired and undesired effects, and individual patient characteristics. Disease models describe the relationship between biomarkers and clinical outcomes, time course of disease and placebo effects. The trial models describe the inclusion/exclusion criteria, patient dis-continuation and adherence. Typical focus of Pharmacometrics has been on drug models, also referred to by terms such as: concentration-effect, dose-response, PKPD relationships. These Pharmacometric analyses are designed, conducted and presented in the context of drug development, therapeutic and regulatory decisions. The single-most important strength of such analyses is its ability to integrate knowledge across the development program and compounds, and biology\(^{[22]}\).
3.2 Population pharmacokinetics

Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest. Certain patient demographical, pathophysiological, and therapeutical features, such as body weight, excretory and metabolic functions, and the presence of other therapies of drugs eliminated mostly by the kidney are usually greater in patients suffering from renal failure than they are in patients with normal renal function who receive the same drug dosage. Population pharmacokinetics seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified\(^{[23-31]}\).

Using the population PK approach in drug development offers the possibility of gaining integrated information on pharmacokinetics, not only from relatively sparse data obtained from study subjects, but also from relatively dense data or a combination of sparse and dense data. The population PK approach allows the analysis of data from variety of unbalanced designs as well as forms of pharmacokinetic analysis, such as concentration data obtained from pediatric and elderly patients, or data obtained during the evaluation of the relationships between dose concentration and efficacy or safety\(^{[23-31]}\).

The subjects of traditional pharmacokinetic studies are usually healthy volunteers or highly selected patients, and average behavior of a group has been the main focus of interest. interindividual variability in pharmacokinetics has been viewed by many as a factor that needs to be minimized, often through complex study designs and control schemes, or though restrictive inclusion/exclusion criteria. In fact, the information on the variability that will occur during clinical use is critical and it is obscured by these restrictions. Moreover, focusing on a single variable in a traditional pharmacokinetic study makes it difficult to study interactions among variables\(^{[23-31]}\).
In contrast to traditional pharmacokinetic evaluation, the population PK approach encompasses so or all the following features:

1. The collection of relevant pharmacokinetic information in patients who are representative of target population to be treated with a drug.
2. The identification and measurement of variability during drug development and evaluation
3. The explanation of variability by identifying factors of demographic and pathophysiological, environmental or concomitant drug-related origin that may influence the pharmacokinetic behavior of a drug.
4. The quantitative estimation of the magnitude of the unexplained variability in the patient population

The magnitude of unexplained variability is important because the efficacy and safety of a drug may decrease as unexplainable variability increases. In addition to interindividual variability, the degree to which steady-state drug concentrations in individuals typically vary about their long-term average is also important. Concentrations may vary due to inexplicable day-to-day or week-to-week kinetic variability and/or due to errors in concentration measurements. Estimates of this kind of variability are important for therapeutic drug monitoring. Knowledge of the relationship among concentrations, response and physiology is essential to design of dosing strategies for rational therapeutics that may not necessarily require therapeutic drug monitoring.

Defining the optimum dosing strategy for a population, subgroup, or individual patient requires resolution of the variability issues discussed above. Recognition of the importance of developing optimum dosing strategies has led to a surge in the use of the population PK approach in new supplements. Population pharmacokinetics can be useful in the drug developments process and should be considered where appropriate.
The model development process is described schematically in the following figure.

Figure 7: Model development process
3.3 Population pharmacokinetic analysis

Population pharmacokinetic modeling is a scientific field that tries to describe biological aspects in a mathematical way. Models are used to characterize inter- and intra-individual variability among subjects. The method that is used for the development of such a model is called Nonlinear Mixed-Effects Modeling and NONMEM software is the tool. A population pharmacokinetic model is consisted of the structural model, the fixed effects and the random effects\[^{32}\].

3.3.1 Structural model

Structural model are the basic equations that are used to describe the pharmacokinetic parameters (i.e. clearance, volume of distribution). The pharmacokinetic parameters are called descriptors. This mathematical representation is the first step for building a model\[^{32}\].

3.3.2 Fixed effects

Fixed effects are the observable properties of individuals that cause the descriptors vary across the population\[^{32}\].

3.3.3 Random effects

Random effects are the effects that can’t be predicted in advance when we are dealing with biological data. There are two sources of randomness. The first is related with the inter-individual or between the subject variability. It is the biological variability that is encountered among the patients. The second one is the intra-individual or within the subject variability. This includes the experimental errors\[^{32}\].
3.4 Simulations

Simulation is a useful tool to provide convincing objective evidence of the merits of a proposed study design and analysis. Simulating a planned study offers a potentially useful tool for evaluating and understanding the consequences of different study designs. Shortcomings in study design result in the collection of uninformative data. Simulation can reveal the effect of input variables and assumptions on the results of a planned population PK study. Simulation allows study designers to assess the consequences of the design factors chosen and the assumptions made. Thus, simulation enables the pharmacometrician to better predict the results of a population PK study and to choose the study design that will best meet the study objectives. A simulation scheme should entail repetitive simulation and appropriate analysis of data sets to control for the effect of sampling variability on parameter estimates. Alternative study designs may be simulated to determine the most informative design[37].

3.5 Optimization of experimental design

Nowadays optimization of experimental design may be considered the initial step, before the performance of an experiment. The profits of such an approach is the reduction of the cost the period and amount of subjects that are demanding for the conduction of a trial. Moreover inadequate study designs frequently leads to vague conclusions. Many softwares and statistical methods can be used for that purpose with obvious benefits[37].

Root mean square error (RMSE) or root mean square deviation (RSMD) is one of the most frequently reported measures of misfit/fit in application of structural application modeling. It is a quadratic scoring rule which measures the average magnitude difference between values predicted by a model and values that actually observed from the environment that is being modeled. These individual differences are also called residuals, and RMSE serves to aggregate them into a single measure of predictive power[37].
The formula that is used for estimating the RMSE is introduced hereby:

\[
RMSE = \sqrt{\frac{\sum_{i=1}^{n} (X_{\text{obs}} - X_{\text{modeli}})^2}{n}}
\]  

\((2)\)

\(X_{\text{obs}}\): observed values

\(X_{\text{model}}\): modelled values at time/place \(i\).

\(n\): number of samples

Relative error (RE) is defined as the absolute error divided by the true value. It is noteworthy that absolute error is the difference between the magnitude of the true value and the observed one that give us the exact number with the units of the quantity that is deviated from the true value. Relative error is expressed as percentage that helps us to calculate the ratio between absolute error and true value. It is useful for validating the precision of the validating parameters\(^{[37]}\).

The formula that is used for estimating the RE is introduced hereby:

\[
RE = (X - X0) / X
\]

\((3)\)

\(X\): true value of a quantity

\(X0\): observed value of the quantity

\(X-X0\): absolute error
Purpose
Part II
The main objective was to identify potential pharmacokinetic interactions between the antifungal and the anticancer agents, which may lead to altered pharmacological or toxicological effect. For that purpose a structural population pharmacokinetic model that predicts the concentration of voriconazole with and without cytarabine was developed. The model was used to optimize the dose when voriconazole is administrated as one hour intravenous infusion. The final goal is the design of the clinical protocol in order to validate the theoretical population pharmacokinetic model. For that reason the evaluation of the time points that will be used to estimate sufficiently the pharmacokinetic parameters of our interest is crucial.
Materials & Methods

Part III
1. Therapeutic protocol—Current clinical practice

Treatment of the newly diagnosed patient with AML is divided into two faces, induction and consolidation therapy according to the guidelines. During the induction chemotherapy cytarabine is administrated a continuous intravenous infusion for seven days in conjunction with idarubicin for three days. During the consolidation therapy patients receive cytarabine and indarubicin in doses similar to those given initially, but for five and two days, respectively. The therapeutic protocol comprises six cycles in a period of five weeks (figure 8).

Due to the toxic effects of chemotherapy, including increased risk of fungal infections; susceptible patients receive prophylactically voriconazole simultaneously with the antitumor therapy. The dosage regimen of voriconazole is one hour intravenous infusion for fourteen consecutive days.

Figure 8: Therapeutic protocol of acute myeloid leukemia
2. Literature review

Project initial steps are assiduous literature review. The available information for each drug should be collected and elaborated. According to the available information the project will be further developed.

Firstly pharmacokinetic and pharmacodynamic information related to voriconazole, cytarabine and idarubicin should be found. Based on this information we will be able to characterize if any worthwhile drug interactions that take place between these three drugs should be investigated. Moreover an initial estimation of the severity of this interaction could be made. Equations that describe that interactions are substantial. This step is considered fundamental as inferences will be made on the development of the project.

Secondly published population pharmacokinetic models of the three drugs should be found. By using these models the plasma concentrations of population related to the doses could be estimated. The modification of these models will provide us with information on how the plasma concentrations are changing and on the risk of patients develop further toxicity of sub-therapeutic effects after the co-administration of the antifungal regimen and the antitumor drugs.

Last but not least the developed pharmacokinetic models will give us the capability on optimizing the experimental design. Statistical methods should be found in order to optimize the time schedule. The developed models should be validated by a small cohort of patients. For that purpose presided time points that estimate with precision and accuracy the time points should be selected.

In conclusion literature research is a tedious but fundamental step for that project. Based on the information that already exist we will be able to infer the clinical outcome after the co-administration of the previous referred drugs. R 3.02 and NONMEM 7.2.0 softwares are the tools that were used for the conduction of simulations and estimations and graphical representation.
Results
Part IV
1. Voriconazole

Voriconazole is a broad spectrum, triazole antifungal agent that is indicated in adults and pediatric patients aged two years old and above. Voriconazole indications include the treatment of invasive aspergillosis, candidemia in non-neutropenic patients, fluconazole-resisant serious invasive Candida infections, fungal infections caused by Scedosporium spp. and Fusarium spp. The drug should be administered primarily to patients with progressive, possibly life-threatening infections.

![Voriconazole structural formula](image)

**Figure 9**: Voriconazole structural formula

The primary mechanism of action of voriconazole is the inhibition of cytochrome P-450 mediated 14 alpha-lanosterol demethylation an essential step in fungal ergosterol biosynthesis. Probably the loss of ergosterol that take place in the fungal cell membrane structure provides to voriconazole its antifungal properties.

The pharmacokinetics of the drug are non-linear due to saturation of its metabolism. When it is administrated orally it is rapidly and almost completely absorbed without affecting by changes in gastric pH. The maximum plasma concentrations (Cmax) achieved one or two hours after the dosing. Voriconazole is distributed extensive into tissues and the volume of distribution (Vd) is estimated to be 4.61/kg when steady state has achieved. It is metabolized by the hepatic cytochrome P450 isoenzymes CYP2C19, CYP2C9 and CYP3A4 and
it is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. The elimination half-life of voriconazole is approximately 6h.

Regarding the adverse reactions, hypersensitivity, QT interval prolongation, hepatic toxicity, visual adverse reactions such as blurred vision and nephrotoxicity are considered the most common side effects that are correlated with the administration of the drug.

2. Cytarabine

Cytarabine is an antineoplastic agent that is used alone or in combination for induction of remission and/or maintenance in patients with acute myeloid leukemia, acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, acute lymphocytic leukemia, erythroleukaemia, blast crises of chronic myeloid leukemia, diffuse histiocytic lymphomas, meningeal leukemia and meningeal neoplasms.

![Cytarabine structural formula](image)

**Figure 10**: Cytarabine structural formula

Cytarabine (ARA-C) is metabolized in vivo to ARA-CTP phosphorylated compound. This competitively inhibits DNA polymerase and may also inhibit certain acid kinase enzymes. Primarily the drug acts as a false nucleoside and competes for enzymes involved in the conversion of cytidine nucleotide to deoxycytidine nucleotide and also incorporation
into the DNA. Cytarabine has no effect on non proliferating cells nor on proliferating cells unless in the S phase. It is a cell cycle specific antineoplastic drug.

After an intravenous injection cytarabine is distributed widely and rapidly into tissues and fluids. The maximum concentration (Cmax) is achieved in 20-60min and the volume of distribution (Vd) is estimated around 2.6L/kg. It is metabolized primarily by the liver and the kidneys and is extracted urinally. The elimination half life is estimated to 1-3h.

3. Idarubicin

Idarubicin is an antineoplastic anthracycline for intravenous use. It is an antileukemic drug that belongs to the family of drugs that called antitumor antibiotics.

![Idarubicin structural formula](image)

**Figure 11**: Idarubicin structural formula

Idarubicin hydrochloride is a DNA-inthercalating analog of daunorubicin which has an inhibitory effect on nucleic acid synthesis and interact with the enzyme topoisomerase II. The high lipophilicity of the compound results in an increased rate of cellular uptake compared with other anthracycline.
Regarding the pharmacokinetics the elimination rate is very slow with an estimated half-life 22 hours. The elimination of the primary active metabolite idarubicinol, has an estimated mean terminal half-life that exceeds 45 hours. The high volume of distribution reflects to the extensive tissue binding. The percentages of idarubicin and idarubicinol bound to human plasma proteins averaged 97% and 94% respectively. The primary active metabolite of idarubicin is idarubicinol which has cytotoxic activity. The drug is eliminated predominately by biliary and to a lesser extent by renal excretion.

4. Drug-Drug Interactions between the antitumor regimens and the antifungal agent

Voriconazole, cytarabine and idarubicin are substrates and/or inhibitors of the same isoenzymes of the cytochrome P450. The drug-drug interaction between voriconazole and the antitumor agents (cytarabine, idarubicin) is characterized as reversible competitive metabolic inhibition. The substrate affinity (Km) and the inhibition potency (Ki) of each drug are represented in the following table[^36].

Table 6: Inhibition potency (Ki) and Substrate affinity (km) of cytarabine idarubicin and voriconazole

<table>
<thead>
<tr>
<th></th>
<th>cytarabine</th>
<th>idarubicin</th>
<th>voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Substrate</td>
<td>Inhibition</td>
<td>Substrate</td>
</tr>
<tr>
<td></td>
<td>Affinity</td>
<td>Potency</td>
<td>Affinity</td>
</tr>
<tr>
<td></td>
<td>(Km)</td>
<td>(Ki)</td>
<td>(km)</td>
</tr>
<tr>
<td>2C9</td>
<td>-</td>
<td>-</td>
<td>17μM</td>
</tr>
<tr>
<td>3A4</td>
<td>319,25μM</td>
<td>6,6μM</td>
<td>-</td>
</tr>
</tbody>
</table>
As we can notice plasma concentration of voriconazole may be affected only by the presence of cytarabine. Both are substrates and inhibitors of the same isoenzyme CYP3A4. Due to the reversible metabolic inhibition maximum metabolic rate remains the same in contrast with the substrate affinity that is reduced (figure 12).

![Figure 12](image)

**Figure 12**: (a) metabolic rate in different types of inhibition (b) slope in different types of inhibition

It is known that the percentage of competitive inhibition is described by the following equation:

$$\% inhibition = \frac{[I]/Ki}{1+[I]/Ki+[S]/Km}$$  \hspace{1cm} (4)

Moreover inhibitory risk can be characterized as high, medium or low according to the ratio $[I]/Ki$ where $Ki$ is the enzyme-inhibitor dissociation constant and $[I]$ is the concentration of inhibitor achieved in vivo. When the ratio exceeds 1, the risk of inhibition is high, while for ratios between 0.1 and 1 the inhibitory risk is considered medium. For ratios less than 0.1 the inhibitory risk remains low.

Regarding to the above ratio and by taking into consideration the therapeutic range of cytarabine (0.001-1mg/L) the inhibitory risk of voriconazole when we co-administrate...
cytarabine ranges from 0.0014 to 0.28. As a consequence the inhibition risk is characterized as low or medium. It was estimated that when plasma concentration of cytarabine exceeds 0.0352mg/L the inhibition risk of voriconazole is medium.

Voriconazole follows michaelis menten elimination. The metabolic rate during its interaction with cytarabine is possible to be re-estimated by the following equation:

\[ V = \frac{V_{\text{max}} \times S}{K_m (1 + I/K_i) + S} \]  

(5)

This equation was embedded in the initial population pharmacokinetic model of voriconazole and attempts to re-estimate the parameters and plasma concentration of voriconazole were conducted.

5. Population pharmacokinetic model of voriconazole

The population pharmacokinetic model of voriconazole was obtained from the literature. The data was collected from 64 adults. The population pharmacokinetic model that best describes the course of voriconazole in humans is a three compartmental model and the parameters that were introduced in the model are the first-order rate constant that connect the gut with the central compartment \( K_a \) the maximum rate of enzyme activity of voriconazole \( V_{\text{max}} \), the concentration of voriconazole were clearance is half maximal \( K_m \), the first-order intercompartmental rate constants connecting the central and peripheral compartments \( K_{cp} \) and \( K_{pc} \), the bioavailability \( F \) and the absorption time \( \text{Lag} \). No covariates were embedded. Simulations were conducted by using NOMEM software, version 7.2. R software was used for statistical and graphical purposes\textsuperscript{[34]}. 
dX(1)/dt = -K_a × X(1)

dX(2)/dt = -[(V_{max}/(K_m×Volume+X(2) + K_Φ)]×X(2) + K_a×X(1)+K_{pc}×X(3)+R(1)

dX(3)/dt = K_Φ×X(3)-K_{pc}×X(3)

X(1), X(2), X(3): the amount of voriconazole in the gut, central compartment and peripherical retrospectively (in milligrams)

K_a: first-order rate constant connecting the gut with the central compartment

V_{max}: maximum rate of enzyme activity in voriconazole (mg/h)

K_m: concentration of voriconazole in the central compartment at which clearance is half-maximal

K_Φ, K_{pc}: first-order intercompartmental rate constants

**Table 7:** Population pharmacokinetic parameters of voriconazole

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ka (h^{-1})</td>
<td>9.77</td>
<td>3.85</td>
<td>10.30</td>
</tr>
<tr>
<td>Vmax (mg/h)</td>
<td>37.67</td>
<td>37.38</td>
<td>11.19</td>
</tr>
<tr>
<td>Km (mg/liter)</td>
<td>2.07</td>
<td>2.28</td>
<td>1.11</td>
</tr>
<tr>
<td>Vol (liter)</td>
<td>149.11</td>
<td>76.65</td>
<td>173.49</td>
</tr>
<tr>
<td>Kcp(h^{-1})</td>
<td>2.01</td>
<td>0.44</td>
<td>3.33</td>
</tr>
<tr>
<td>Kpc(h^{-1})</td>
<td>9.35</td>
<td>2.14</td>
<td>11.68</td>
</tr>
<tr>
<td>F</td>
<td>0.86</td>
<td>0.91</td>
<td>0.13</td>
</tr>
<tr>
<td>Lag (h)</td>
<td>1.12</td>
<td>0.77</td>
<td>0.99</td>
</tr>
</tbody>
</table>
The population pharmacokinetic model of cytarabine was obtained from the literature too. Twenty-four new patients diagnosed with acute myeloid leukemia were included in the study. The population pharmacokinetic model that best describes the course of cytarabine in humans is a two compartmental model and the parameters that were introduced in the model are the clearance (CL) the central volume ($V_c$), the intercompartmental clearance (Q) and the peripheral volume ($V_p$). The baseline white blood cell count (CL-Bwbc) was considered as covariate. Simulations were conducted by using NOMEM software, version 7.2. R software was used for statistical and graphical purposes\cite{35}.

Figure 13: Voriconazole compartmental model.

6. Population pharmacokinetic model of cytarabine
$$V_{Pi} = \theta_p \times e^{\eta_i} \times (1 + \theta_j \times (COV_i - \text{median}_{covi}))$$

$V_{pi}$: individual value of the population parameter $P$

$\theta_p$: the estimate for the median patient

$e^{\eta_i}$: the exponential function that describes the interindividual variability

$\theta_j$: parameter estimate describing the change in the PK parameter for an individual with covariate $COV_i$

**Table 8**: Inhibition potency ($K_i$) and Substrate affinity ($k_m$) of cytarabine idarubicin

<table>
<thead>
<tr>
<th>Population pharmacokinetics</th>
<th>TVP (RSE %)</th>
<th>IIV CV% (RSE %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>272 (1.9)</td>
<td>45 (5.3)</td>
</tr>
<tr>
<td>$V_c$ (L)</td>
<td>62.8 (2.5)</td>
<td>70 (5.2)</td>
</tr>
<tr>
<td>$Q$ (L)</td>
<td>13.7 (4.1)</td>
<td></td>
</tr>
<tr>
<td>$V_p$ (L)</td>
<td>75.4 (32)</td>
<td></td>
</tr>
<tr>
<td>Res. Error (%)</td>
<td>75.7 (13)</td>
<td></td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL-bWBC</td>
<td>-0.0020 (5.1)</td>
<td></td>
</tr>
</tbody>
</table>
The population pharmacokinetic model of voriconazole after drug drug interaction with cytarabine was developed. For that purpose the initial model of voriconazole was modified. The model that describes the drug-drug interaction is a two compartmental model. The compartment that is referred as gut was excluded as the drug is administrated intravenously. For the same reason the the first-order rate constant that connect the gut with the central compartment (Ka),the bioavailability (F) and the absorption time (Lag) weren’t taken into account. Finally the the concentration of voriconazole were clearance is half maximal (Km) was modified according to the following equation. The rest parameters remained the same. Simulations were conducted by using NOMEM software, version 7.2. R software was used for statistical and graphical purposes.
\[
dX(1)/dt= -\left(\frac{V_{\text{max}}}{(K_m(1+I/K_i)\times \text{Volume} + X(1)) + K_\Phi}\right)\times X(1) + K_\alpha \times X(1) + K_{pc} \times X(2) + R(1)
\]
\[
dX(2)/dt= K_\Phi \times X(2) - K_{pc} \times X(2)
\]

\(X(1), X(2)\): the amount of voriconazole in the central compartment and peripheral retrospectively (in milligrams)

\(V_{\text{max}}\): maximum rate of enzyme activity in voriconazole (mg/h)

\(K_m\): concentration of voriconazole in the central compartment at which clearance is half-maximal

\(K_\Phi, K_{pc}\): first-order intercompartmental rate constants

\(I\): concentration of inhibitor

\(K_i\): inhibition potency of the inhibitor

**Figure 15**: Voriconazole compartmental model after intravenous infusion
8. Assumptions and limitations of the developed population pharmacokinetic model of voriconazole

It is worth mentioning that the model that was developed is a theoretical model. For that before conducting simulations, the assumptions and eliminations that are introduced below should be taken into account.

- No variability of inhibition potency (Ki) of cytarabine was included in the model due to the lack of data
- The in vitro parameter of inhibition potency (Ki) is considered representation of the in vivo process
- Plasma concentration at steady state of both drugs were assumed to reflect liver tissue concentrations for the purpose of our analysis
- Because of the way of administration of cytarabine (iv infusion/24h) the plasma concentrations of the antitumor agent are not affected by the presence of voriconazole
- To evaluate clearance inhibition median cytarabine concentrations were used as a constant in the model
- The concentrations of the antifungal agent due to prophylactic therapy should remain in the therapeutic range.
9. Simulations and estimations

Initially the range of voriconazole blood concentrations should be specified. The therapeutic range is between 1 and 5.5mg/L. As maximum nontoxic concentration was taken the 5.5mg/L. Moreover, regarding the literature all patients that had minimum concentration level above 2.05mg/L had the favorable results. This is the threshold concentration that was used to indicate the number of patients that were susceptible to sub-therapeutic effects.

One thousand patients were simulated and the pharmacokinetic profile of voriconazole and cytarabine was obtained. The graphs represent the 95% confidence interval (dashed line) for the mean and the median (solid line) among the patients for both drugs. The shaded area depicts the therapeutic range. The results indicate that, regarding the administrative doses, voriconazole exceeds the limits of its therapeutic range (1-5.5mg/L) in some patients. 145 patients out of 1000 patients exceed the therapeutic range. As a consequence toxic effects may be developed solely by the antifungal agent. On the other hand cytarabine plasma concentrations are lying in the therapeutic range (0.001-1mg/L). That leads to the conclusion that cytarabine solely don’t participate to the development of toxicity.
Figure 16: Pharmacokinetic profile of voriconazole after one hour intravenous infusion for fourteen consecutive days. The dashed lines represent the 95% confidence interval of the mean and the solid line the mean. The shade area depicts the therapeutic range of voriconazole.

Figure 17: Pharmacokinetic profile of cytarabine after twenty four hours intravenous infusion for seven consecutive days. The dashed lines represent the 95% confidence interval of the mean and the solid line the mean.
The next step was to characterize the drug-drug interaction that take place among voriconazole and cytarabine and evaluate if that kind of interaction increases the toxicity among patients. As cytarabine is administrated intravenous for seven consecutive days we made the assumption that voriconazole does not affect the levels of plasma concentration of cytarabine. For that purpose only the model that describe the effects of cytarabine to voriconazole was used. The simulations that were conducted indicate that 191 patients out of 1000 who receive voriconazole were above the therapeutic range after the co-administration of cytarabine (0.03mg/L).

The following graphs illustrate the 95% confidence interval (dashed line) for the mean and the median (solid line) among the patients for both drugs. The shade area depicts the therapeutic range. The administrated doses are 6, 5.5 and 5mg/kg/1h respectively. It is highly noticeable that the number of patients that exceed the therapeutic range is reduced by reducing the dose. The tables 9 and 10 represent the exact number of patients that were simulated; the number that exceeds the 5.5mg/; the number that is below the threshold of 2.05mg/L; and the median of the concentrations in different doses and different dose schemes. According to those tables the optimal dose was chosen to be the 5mg/kg/1h.
Figure 19: Number of simulated patients above the therapeutic range or below 2.05mg/L in different doses 6, 5.5 and 5mg/Kg/1h respectively. The dashed lines represent the 95% confidence interval of the mean and the solid line the mean. The shade area depicts the therapeutic range of voriconazole.
**Table 9:** Number of simulated patients above the therapeutic range or below 2.05mg/L in different dose regimens.

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole (6mg/kg/1h) and Cytarabine</th>
<th>Voriconazole (5.5mg/kg/1h) and Cytarabine</th>
<th>Voriconazole (5mg/kg/1h) and Cytarabine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of simulated patients</strong></td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Number of patients above the therapeutic range (5.5mg/L)</strong></td>
<td>145</td>
<td>191</td>
<td>130</td>
</tr>
<tr>
<td><strong>Number of patients below 2.05mg/L</strong></td>
<td>175</td>
<td>130</td>
<td>145</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>2.93625</td>
<td>3.32425</td>
<td>2.9254</td>
</tr>
</tbody>
</table>

**Table 10:** Number of simulated patients above the therapeutic range or below 2.05mg/L in different dose regimens.

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole (6mg/kg/1h) and Cytarabine</th>
<th>Voriconazole (6mg/kg/1.5h) and Cytarabine</th>
<th>Voriconazole (6mg/kg/2h) and Cytarabine</th>
<th>Voriconazole (5mg/kg/2h) and Cytarabine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of simulated patients</strong></td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Number of patients above the therapeutic range (5.5mg/L)</strong></td>
<td>191</td>
<td>187</td>
<td>186</td>
<td>70</td>
</tr>
<tr>
<td><strong>Number of patients below 2.05mg/L</strong></td>
<td>130</td>
<td>141</td>
<td>142</td>
<td>300</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>3.32425</td>
<td>3.2618</td>
<td>3.24705</td>
<td>2.531</td>
</tr>
</tbody>
</table>
10. Optimization of experimental design

The next step was to evaluate if the time points (2, 26, 27, 50, 51, 120, 335, 336) that are already used are able to estimate the parameters of Volume of distribution ($V_d$) and Maximum metabolic rate accurately and precisely. Relative Error (RE) and Root Mean Square Error (RMSE) are the statistical methods that are used for that purpose. The results are representing in the following figures. In addition a table that has the exact estimated values is included. New time points (168, 193, 219, 245, 271, 297, 323, 349) based on the pharmacokinetic profile of voriconazole were selected. The number of the time points and the number of subjects was kept the same. According to our results the new time points were able to estimate the pharmacokinetic parameters more accurate. In both cases the time points weren’t able to estimate the time points precisely.

Figure 20: Optimization of experimental design process
Figure 21: (a) precision of estimated parameters of initial time points (root mean square error) (b) accuracy of estimated parameters of the initial time points (relative error)
Figure 22: (a) precision of estimated parameters of feasible selected time points (root mean square error) (b) accuracy of estimated parameters of the feasible selected time points (relative error).
Table 11: Root mean square error and relative error values

<table>
<thead>
<tr>
<th></th>
<th>KM</th>
<th>VM</th>
<th>V1</th>
<th>K12</th>
<th>K21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial time points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSMEmean</td>
<td>0.35</td>
<td>0.0224</td>
<td>0.343</td>
<td>0.823</td>
<td>0.618</td>
</tr>
<tr>
<td>RSMEci</td>
<td>0.00191</td>
<td>0.00242</td>
<td>0.00191</td>
<td>0.00242</td>
<td>0.00191</td>
</tr>
<tr>
<td>Remean</td>
<td>-11.7</td>
<td>0.747</td>
<td>11.4</td>
<td>-27.4</td>
<td>-20.6</td>
</tr>
<tr>
<td>Resd</td>
<td>0.315</td>
<td>0.249</td>
<td>2.02</td>
<td>13.2</td>
<td>6.75</td>
</tr>
<tr>
<td><strong>New time points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSMEmean</td>
<td>0.29</td>
<td>0.000681</td>
<td>0.298</td>
<td>0.926</td>
<td>0.766</td>
</tr>
<tr>
<td>RSMEci</td>
<td>0.00697</td>
<td>0.0172</td>
<td>0.00697</td>
<td>0.0172</td>
<td>0.00697</td>
</tr>
<tr>
<td>Remean</td>
<td>-13</td>
<td>-0.0305</td>
<td>13.3</td>
<td>-41.4</td>
<td>-34.3</td>
</tr>
<tr>
<td>Resd</td>
<td>1.38</td>
<td>0.561</td>
<td>6.93</td>
<td>40.4</td>
<td>26.6</td>
</tr>
</tbody>
</table>
Patients with acute myeloid leukemia that are susceptible for fungal infections receive prophylactically voriconazole. Pharmacokinetic interactions between voriconazole, cytarabine and idarubicin affect the pharmacokinetic profile of the drugs and as a consequence their toxicological or therapeutical profile. Voriconazole is not affected by idarubicin. The reversible competitive inhibition that take place between voriconazole and cytarabine involving the CYP3A4 enables the amendment of the doses in order to achieve the optimal therapeutic outcome. Because of the michaelis-mentel elimination that both drugs follow an equation that describes the changes to the metabolic rate was feasible to be introduced to the initial model of voriconazole. The variability of the pharmacokinetic parameters was kept the same. No variability related to the inhibition potency of voriconazole was included in the model. As cytarabine is administrated as twenty four hours intravenous infusion for seven consecutive days we made the assumption that the presence of voriconazole does not affect the plasma concentration of cytarabine and as a consequence the pharmacokinetic profile of the drug remains the same. On the other had voriconazole plasma concentration is changing due to the presence of cytarabine. According to the structural model that was developed for characterizing the drug-drug interactions that take place when we co-administrate the antifungal agent and the antitumor regimen the pharmacokinetic profile of voriconazole is changing. Our purpose was to change the dose scheme in order to keep the pharmacokinetic profile of voriconazole. Different trials were conducted by modifying the dose and the rate of infusion of voriconazole. The optimal dose scheme is considered to be 5mg/Kg one hour intravenous infusion. It is worth mentioning that the assumption, that the optimal prophylactic concentrations should be between the therapeutic range of voriconazole was taken as there are no guidelines to indicate how to administrate voriconazole prophylactically as one hour intravenous infusion. By following that regimen less patients exceed the therapeutic range. Moreover the number of patients that has the favorable therapeutic results is almost the same.
The next step was to validate if the time that were used to a previous experiment are efficient for estimating the pharmacokinetic parameters of our interest accurate and precisely. In addition new time points were selected according to the pharmacokinetic profile of voriconazole after one hour intravenous infusion for fourteen consecutive days for subsequent. The time points were selected after the achievement of steady state of voriconazole. Time points were picked at the peak, trough, distribution phase and elimination phase. It is worth mentioning that the accuracy was able to be optimized in contrast with efficiency of the time points to estimate precisely the pharmacokinetic parameters of our interest. That is probably caused due the high level of interindividual variability that can’t be estimated from our model. To sum up the time points from the previous experiment can be efficiently be used for the purposes of that experiment.

Furthermore the pharmacokinetic model allowed the simulation of patient data to test the effect of dose adjustment scenarios. The next step is to validate and improve the model by conducting a small clinical trial. A small cohort of 20 patients and the investigated time points (2, 26, 27, 50, 51, 120, 335, 336h after the administration of voriconazole) could be used for the experiment. If the model is valid, it could be used in different dose schemes. Future prospective is to develop a population pharmacokinetic model for idarubinine and try to characterize the drug-drug interactions that take place between idarubicie and voriconazole. For that purpose, analytical methods for extracting, separating and detecting voriconazole, cytarabine and idarubicine from blood samples were validated. A case report file (CRF) was written according to the demographic characteristics, the co-administrated drugs, the outcome and the toxic effects after the co-administration of the antifungal agent and the antitumor regimes.

Patients will be included to the investigation according to the following criteria:

1. Adult patients aged ≥ 18 years.
2. State capacity by WHO ≤ 2.
3. Patients with AML or de novo, or after preceding MDS high-grade malignancy, which is to receive chemotherapy induction or consolidation / amplification with combinations of chemotherapeutic drugs mentioned above

4. Normal renal function, as evidenced by assessing serum creatinine levels ≤ 2 mg/dl or creatinine clearance > 50 ml/min.

5. Normal liver function, as evidenced by the existence of normal levels or elevated serum transaminases less than twice the upper limit of normal value and serum bilirubin <2 mg/dl.

6. Absence of active systemic acute or chronic viral infection that affects your liver function, such as HAV-, HBV-, HCV-, CMV- and HIV- infection.

7. Absence of chronic disease that requires systemic therapy with anticonvulsants, antiarrhythmics, anticoagulants, antiretroviral and non-steroidal anti-inflammatory drugs.

8. Lack of active neoplastic disease other than: basal skin epithelioma, papillary thyroid carcinoma, non-metastatic prostate cancer (Gleason score ≤ 6), in situ carcinoma of the uterine cervix, carcinoma in situ breast.

9. Lack of active uncontrolled psychiatric illness, which makes problematic patient cooperation.

10. Written consent of the patients informed about participation in the study.

On the other hand patients will be excluded from the investigation if one of the criteria that are represented below is present:

1. Coexistence and other active neoplastic disease, with the following exception: basal skin epithelioma, papillary thyroid carcinoma, non-metastatic prostate cancer (Gleason score ≤ 6), in situ carcinoma of the uterine cervix, carcinoma in situ breast.

2. Performance status at WHO > 2.

3. Severe renal impairment, as this will be evidenced by stable serum creatinine > 2 mg/dl in successive measurements.
4. Severe hepatic impairment, as may arise from serum bilirubin value > 2 mg/dl and/or values of transaminases greater than twice the upper limit of normal or established liver failure/cirrhosis.

5. Active chronic systemic viral disease that affects the liver function, such as HAV-, HBV-, HCV-, CMV- and HIV-infection.

6. History of drug abuse or alcohol in the past 12 months.

7. Other chronic disease that requires systemic therapy with anticonvulsants, antiarrhythmics, anticoagulants, antiretroviral and non-steroidal anti-inflammatory drugs.

8. Presence of active psychiatric disorder or a situation in investigator judgment impedes the smooth cooperation of the patient.

9. Inability or refusal of the patient to participate in the study or to give written informed consent.

Last but not least the population pharmacokinetic model that was developed could be used for the optimization of drug therapy when we have identified fungal infections. Based on the same principles similar models for characterizing the drug-drug interactions that take place between cytarabine, idarubicin, itraconazole and fluconazole can be developed. This could improve the clinical outcome of patients with acute myeloid leukemia by reducing the drop outs of the patients due to toxicity or subtherapeutic effects.
Conclusion
Part VI
The pharmacokinetic model allowed the simulation of patient data to test the effect of dose adjustment scenarios. The next step is to validate the model using a small cohort of patients. The sample time points to be investigated correspond to those evaluated in the simulations. The benefit of such an approach is that the new dose regimen of voriconazole that leads to the reduction of drop outs can be re-estimated by using the minimum number of subjects. Last but not least the optimization of the experimental design could improve subsequent experiments.
References

Part VII


Appendix
Part VIII
$SIZES\ NO=500$

$PROBLEM$ VORICONAZOLE

$INPUT$ ID TIME AMT RATE DV MDV EVID CMT II ADDL

$DATA$ sim.csv IGNORE=@

$SUBROUTINES$ ADVAN6 TOL=3

$MODEL$ COMP=(CENTRAL) COMP=(PERIPH)

$PK$

VM = THETA(1) * EXP(ETA(1))
KM = THETA(2) * EXP(ETA(2))
V1 = THETA(3) * EXP(ETA(3))
K12 = THETA(4) * EXP(ETA(4))
K21 = THETA(5) * EXP(ETA(5))
S1 = V1

$ERROR$

IPRED=F
Y = F(1 + ERR(1))

$DES$

DADT(1) = K21*A(2) - K12*A(1) - A(1) * VM / (KM*S1 + A(1))
DADT(2) = K12*A(1) - K21*A(2)

$THETA$

37.67 ; VM
2.07 ; KM
149.11 ; V1
2.01 ; K12
9.35 ; K21

$OMEGA$

0.0967 ; VM
0.2091 ; KM
0.0338 ; V1
0.206 ; K12
0.100 ; K21

$SIGMA$

0.96
$PROBLEM CYTARABINE
$INPUT ID TIME AMT RATE DV MDV EVID CMT bWBC II ADDL
$DATA sim.csv IGNORE=@
$SUBROUTINES ADVAN3 TRANS4
$PK
TVCL= THETA(1)*(1+(THETA(5)*bWBC))
CL  = TVCL*EXP(ETA(1))
TV1 = THETA(2)
V1  = TV1*EXP(ETA(2))
TQ  = THETA(3)
Q   = TQ
TV2 = THETA(4)
V2  = TV2
S1=V1
$error$
IPRED=F
FLAG=0
IF(F.EQ.0) FLAG=1
Y = (1-FLAG)*LOG(F+FLAG) + ERR(1)
$THETA
272 ;CL
62.8 ;V1
13.7 ;Q
74.5 ;V2
-0.0020 ;bWBC
$OMEGA
0.2025 ;CL
0.49 ;V1
$SIGMA
0.96
$SIZES NO=500
$PROBLEM VORICONAZOLE_CYTARABINE
$INPUT    ID TIME AMT RATE DV MDV EVID CMT II ADDL I KI
$DATA sim.csv IGNORE=@
$SUBROUTINES  ADVAN6 TOL=3
$MODEL COMP=(CENTRAL) COMP=(PERIPH)
$PK
VM  = THETA(1)*EXP(ETA(1))
KM  = THETA(2)*EXP(ETA(2))
V1  = THETA(3)*EXP(ETA(3))
K12 = THETA(4)*EXP(ETA(4))
K21 = THETA(5)*EXP(ETA(5))
S1=V1
$ERROR
IPRED=F
Y = F(1 + ERR(1))
$DES
KMI=KM*(1+I/KI)
DADT(1) = RATE + K21*A(2) - K12*A(1) - A(1)*VM/(KMI*S1+A(1))
DADT(2) = K12*A(1) - K21*A(2)
$THETA
37.67   ;VM
2.07    ;KM
149.11  ;V1
2.01    ;K12
9.35    ;K21
$OMEGA
0.0967 ;VM
0.2091 ;KM
0.0338 ;V1
0.206  ;K12
0.100  ;K21
$SIGMA
0.96
# clean up all variables
rm(list=ls(all=TRUE))

# set seed so that each run gives the same effects, also this makes
# running on multiple machines easier
set.seed(5)

# nsbj is the number of subjects
nsbj<-1000
# num_run is the number of runs
num_run<-1
if(num_run<1 || num_run > 300) { break }

# initialization
top_dir <- file.path("C:/AML/CYTVOR0005")
working_dir <- file.path(top_dir)
setwd(working_dir)

# set number of simulations per subject to 1
nsim <- 1

# create dirlisting
cwd <- working_dir
pwd <- working_dir
cur_run <- 0

tim<-seq(from=0,to=336)
ltim<-length(tim)

# while number of iterations < number of times i want to run #while
# (num_run > cur_run){

# cleanup used variables of previous iteration
if(cur_run>0)rm(list="d")

# make new iteration dir
dir.create(file.path(pwd,cur_run))
setwd(file.path(pwd, cur_run))
cwd<-getwd()

# WT is the body weight
WT<-rnorm(nsbj,71.37,13.54)

d <- data.frame(ID=rep(1:(nsbj*nsim), each=ltim))
d$TIME <- tim
d$AMT <- NA #mcg/kg
d$RATE<-NA
d$DV <- NA
d$MDV <- 0
d$EVID<- 0
d$CMT <- NA
d$II<-NA
d$ADDL <-NA
dos <- data.frame(ID=1:(nsbj*nsim))
dos$TIME <- 0
dos$AMT <- 6*WT #mcg/kg
dos$RATE <- 6*WT
dos$DV <- NA
dos$MDV <- 1
dos$EVID <- 1
dos$CMT <- 1
dos$II <- 24
dos$ADDL <- 14

d <- rbind(dos,d)
d <- d[order(d$ID,d$TIME),]

#write simulated csv file
file_nm <- "sim.csv"
write.csv(d,file.path(cwd,file_nm),na=".",quote=FALSE,row.names=FALSE)

#copy nonmem control file to new iteration dir
nonmem_fn <- "voriconazole_sim.mod"
file.copy(file.path(top_dir, nonmem_fn),file.path(cwd))

#read data from nonmem control file
nonmem_file <- readLines(file.path(cwd, nonmem_fn))

#change random seed nonmem with gsub
pos1 <- grep('(123457)',nonmem_file)
nonmem_file[pos1]<-gsub("$SIMULATION (123457) ONLYSIM",
"$SIMULATION (",round(runif(1,1,99999)),") ONLYSIM", sep='')

#write nonmem control file
writeLines(nonmem_file,nonmem_fn)

#execute nonmem
shell(paste("execute ", nonmem_fn, sep=''))

setwd(top_dir)
#goto next
cur_run = cur_run+1
#}
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
<th>Example value</th>
<th>Symbol</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>Amount of drug administered.</td>
<td>500 mg</td>
<td>$D$</td>
<td></td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>Time between drug dose administrations.</td>
<td>24 h</td>
<td>$\tau$</td>
<td></td>
</tr>
<tr>
<td><strong>$C_{\text{max}}$</strong></td>
<td>The peak plasma concentration of a drug after administration.</td>
<td>60.9 mg/L</td>
<td>$C_{\text{max}}$</td>
<td>Direct measurement</td>
</tr>
<tr>
<td><strong>$t_{\text{max}}$</strong></td>
<td>Time to reach $C_{\text{max}}$.</td>
<td>3.9 h</td>
<td>$t_{\text{max}}$</td>
<td>Direct measurement</td>
</tr>
<tr>
<td><strong>$C_{\text{min}}$</strong></td>
<td>The lowest (trough) concentration that a drug reaches before the next dose is administered.</td>
<td>27.7 mg/L</td>
<td>$C_{\text{min,ss}}$</td>
<td>Direct measurement</td>
</tr>
<tr>
<td><strong>Volume of distribution</strong></td>
<td>The apparent volume in which a drug is distributed (i.e., the parameter relating drug concentration to drug amount in the body).</td>
<td>6.0 L</td>
<td>$V_d$</td>
<td>$\frac{D}{C_0}$</td>
</tr>
<tr>
<td><strong>Concentration</strong></td>
<td>Amount of drug in a given volume of plasma.</td>
<td>83.3 mg/L</td>
<td>$C_0, C_{\text{ss}}$</td>
<td>$\frac{D}{V_d}$</td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>The time required for the concentration of the drug to reach half of its original value.</td>
<td>$12\ h$</td>
<td>$t_{1/2} = \frac{\ln(2)}{k_e}$</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>--------</td>
<td>---------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination rate constant</strong></td>
<td>The rate at which a drug is removed from the body.</td>
<td>$0.0578\ h^{-1}$</td>
<td>$k_e = \frac{\ln(2)}{t_{1/2}} = \frac{CL}{V_d}$</td>
<td></td>
</tr>
<tr>
<td><strong>Infusion rate</strong></td>
<td>Rate of infusion required to balance elimination.</td>
<td>$50\ mg/h$</td>
<td>$k_{in} = C_{ss} \cdot CL$</td>
<td></td>
</tr>
<tr>
<td><strong>Area under the curve</strong></td>
<td>The integral of the concentration-time curve (after a single dose or in steady state).</td>
<td>$1,320\ mg/L\cdot h$</td>
<td>$AUC_{0-\infty} = \int_0^\infty C\ dt$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$AUC_{\tau,ss} = \int_t^{t+\tau} C\ dt$</td>
<td></td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>The volume of plasma cleared of the drug per unit time.</td>
<td>$0.38\ L/h$</td>
<td>$CL = V_d \cdot k_e = \frac{D}{AUC}$</td>
<td></td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>The systemically available fraction of a drug.</td>
<td>$0.8$</td>
<td>$f = \frac{AUC_{po} \cdot D_{iv}}{AUC_{iv} \cdot D_{po}}$</td>
<td></td>
</tr>
<tr>
<td><strong>Fluctuation</strong></td>
<td>Peak trough fluctuation within one dosing interval at steady state</td>
<td>$41.8\ %$</td>
<td>$%PTF = \frac{C_{max,ss} - C_{min,ss}}{C_{av,ss}} \cdot 100$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>where $C_{av,ss} = \frac{1}{\tau} AUC_{\tau,ss}$</td>
<td></td>
</tr>
</tbody>
</table>