# Optimizing antifungal treatment through pharmacometrics: dosing considerations to enhance outcome

Chen, L.

# Chapter 1

## General introduction and scope

## 1.1 Invasive fungal diseases

Fungi, a distinct large group of micro-organisms, are ubiquitous in the environment. They are present in the air, soil, on plants and trees, indoor surfaces, and even on human skin, and mucosa [1]. Among approximately 6 million fungal species on Earth, about 0.01% are known to infect humans [2]. Fungi can easily spread to humans by direct or indirect contact, or simply by inhaling fungal conidia from the air. Invasive fungal diseases are diseases caused by fungal infections where fungi invade human tissue, germinate, and establish themselves, resulting in a prolonged illness. Invasive fungal diseases are commonly considered to be a higher severity of systemic and deep-seated fungal infection, even though from a microbiological perspective, a common, local, mild, self-limiting superficial fungal disease can also be invasive [3]. Over 150 million annual cases of severe fungal infections occur worldwide, resulting in 1.7 million deaths every year [4]. The number of people who die from the top 10 invasive fungal diseases is even higher than those dying from tuberculosis [5] or malaria [6]. Despite recent progress in the diagnosis and management of invasive fungal diseases, the mortality rate is still unacceptably high, varying between 20% and 95%, depending on the infection type and the patient population. The most common fungal pathogens are yeasts, such as *Candida spp.* and *Cryptococcus spp.*, and molds, such as *Aspergillus spp.* and *Mucorales spp.*, together accounting for more than 90% of reported fungal-related deaths [7].

As first-line defense humans have skin and mucosal membranes to prevent fungi from invading, as well as immune responses to restrict the spread of the invaded fungi and clear them before they can cause serious illness [8]. Such a defense system can be broken if any of these functions are disturbed. The invasive fungal disease mostly impacts individuals with profound immunodeficiencies, such as hematology patients receiving chemotherapy, intensive care unit patients with viral infection (e.g. influenza or COVID-19) [9, 10], HIV/AIDS patients, patients on immunosuppression, for instance, hematopoietic stem cell or solid organ transplants, patients on long-term glucocorticosteroid therapy, or patients with primary immunodeficiencies such as chronic granulomatous diseases. Among these patients, patients with hematological malignancies such as leukemia and lymphoma are particularly vulnerable to invasive fungal diseases and therefore have been considered the targeted population of the novel antifungal drug development for treating invasive fungal disease (IFD) [11]. Common treatment strategies for hematological malignancies involving antineoplastic chemotherapy, stem cell transplantation, as well as the new targeted and immunotherapeutic therapy [12], often induce neutropenia, which weakens the immune response, thereby increasing the risk of invasive fungal diseases.

## 1.2 Current antifungal treatment options and challenges

The current antifungal treatments are categorized into four groups based on their mechanism of action: polyenes, flucytosine, azoles, and echinocandins. Among

these, azoles are by far the most widely used antifungal agents in preventing and treating fungal infections owing to their broad-spectrum activity. Azoles are fungistatic. They inhibit fungal growth by blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane, by inhibiting the fungal cytochrome P450 enzyme lanosterol 14α-demethylase. Fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole are frequently used triazole antifungals. Even though they are recommended as the first-line prevention or treatment of invasive candidiasis or aspergillosis [13], treatments with triazole antifungals come with a few challenges, including numerous drug-drug interactions via inhibition or induction of human cytochrome P450 (CYP) enzymes (voriconazole and itraconazole), erratic absorption resulting in inadequate exposure (itraconazole tablets and posaconazole oral suspension), saturable metabolism (voriconazole) causing drug accumulation and toxicity, such as QT prolongation (all triazoles), hepatotoxicity (itraconazole and voriconazole and posaconazole), and neurotoxicity (voriconazole). As for all triazoles, exposure-response relationships are established, these factors may impact drug efficacy or toxicity. To address this, it is crucial to understand the pharmacokinetics of triazole agents.

### 1.3 Population pharmacokinetic modeling and simulation

Population pharmacokinetic modeling is a well-established method to describe the concentration-time profile of a drug in the body, in which data from all individuals in a population are analyzed simultaneously using a nonlinear mixed-effects model. “Nonlinear” refers to the nonlinearity of the concentration related to time and model parameters. “Mixed-effects” refers to the combination of two types of parameterization, i.e., “fixed effects” and “random effects”. “Fixed effects” applies to parameters that do not vary across individuals. “Random effects” applies to parameters that vary across or within individuals, which is often referred to as variability [14]. The fixed effects determine the pharmacokinetic profile of the typical individual from the population. The random effect determines how each individual’s pharmacokinetic profile deviates from the typical individual. Covariates in the population pharmacokinetic analysis are variables that are measurable and considered to have a potential relationship with the pharmacokinetic parameters in the model, such as weight, age, sex, race, renal/hepatic function, and concomitant medications. A primary goal of population pharmacokinetic modeling is to screen and quantify the impact of covariates that explain (part of) the inter-individual variability. Once the population pharmacokinetic model is developed, we can use model-based simulations to evaluate and optimize drug dosing. During this process, scenarios with various combinations of relevant covariates can be simulated under the standard dose to identify scenarios that can put patients at risk for overdosing, leading to toxicity, or underdosing, leading to therapeutic failure. Once hazardous scenarios are identified, alternative dosing schemes can be simulated to select and propose an optimal regimen.

In contrast to the non-compartmental pharmacokinetic analysis, population

pharmacokinetic modeling uses more complex mathematical and compartmental methods during model development and optimization, therefore often requires more time and effort. Yet the effort often pays off. Unlike the non-compartmental pharmacokinetic analysis, population pharmacokinetic modeling requires neither a stringent study design nor rich concentration-time data, which enables analyzing clinical data collected in a setting where rich data are not available, such as the concentration data from phase 2 and 3 trials, therapeutic drug monitoring, or opportunistic sampling. In fact, it may even be beneficial for the population pharmacokinetic modeling to have variability in sampling times. As population pharmacokinetic modeling can accommodate flexible study designs, it enables integrating concentration-time data across studies of various sampling schedules, formulations, and populations, to explore new research questions and derive more convincing conclusions by making the maximum use of the available information. For example, many marketed drugs are supplied with multiple formulations while most pharmacokinetic studies only analyze one formulation. With population pharmacokinetic modeling, pharmacokinetic data, regardless of whether rich or sparse, from patients receiving various formulations can be analyzed simultaneously and provide a comprehensive overview of the differences in the pharmacokinetic feature among various formulations. Such a quantified pharmacokinetic overview can provide insight into the pros and cons of each formulation, which serves as a reference for clinicians when prescribing a drug with multiple formulations. In addition, population pharmacokinetic modeling allows the exploration of extrapolation potential from one population to another. In case the extrapolation fails, an integrated analysis combining both populations can provide insights into which pharmacokinetic parameter(s) caused the difference and to what extent they are different from each other.

### 1.4 Oral absorption

Ninety percent of the global market share of drugs intended for humans comes as an oral formulation [15]. It is the most preferred administration route, because of the convenience which yields high patient compliance. Bioavailability is the most important pharmacokinetic parameter for oral absorption, as, together with clearance, it is the main driver of drug exposure. Bioavailability is impacted by many factors, including physicochemical properties of the drug (e.g., particle size, solubility, charge state, and permeability), drug formulation, and (patho)physiological characteristics (e.g., gastrointestinal pH, intestinal motility, and luminal water volumes) which may be impacted by concomitant food intake and biorhythm. As a result, high intra- and interindividual variability are not uncommon for bioavailability. Given that the oral route is the preferred administration route for long-term prophylaxis of invasive fungal diseases and considering the high mortality of breakthrough invasive fungal diseases that may result from under-exposure, bioavailability is of particular importance for these drugs. Therefore, identifying and quantifying factors that explain the variability of bioavailability for the antifungal drugs, is vital to guide adequate and safe dosing,

especially for those oral formulations with erratic absorption.

In theory, nonlinear pharmacokinetics can occur in all processes of absorption, distribution, metabolism, and excretion which involve enzymes or carrier-mediated transport. Intestinal metabolism and interaction with the intestinal transporters are common perpetrators causing saturated absorption. In addition to these, the exposure of poorly soluble weakly basic compounds can also exhibit a less-than-proportional increase with the increasing dose. This is because such compounds often dissolve incompletely in the stomach and the undissolved part subsequently transfers to the small intestine and acts as nuclei/seeds resulting in rapid precipitation under the increased pH, further resulting in unabsorbed drug excretion. In this case, when such compounds are given an increased dose, a higher fraction of precipitation and unabsorbed drug excretion would occur, manifesting a negative dose-dependent bioavailability [16]. If such dose-dependent nonlinear bioavailability is properly captured, dividing the same daily dose into a higher frequency can be a new strategy to ensure effective exposure. However, possibly limited by the narrow range of available dosages, such nonlinearity is rarely characterized in the published pharmacokinetic models. One prime example is posaconazole oral suspension.

Although drug absorption is a very complex process through numerous potential interactions, many published population pharmacokinetic studies adopted simple empirical absorption models with the assumptions of zero or first-order absorption rate with or without lag time. This is partly because for many marked oral drugs, the absorption is rather fast and the samples collected during the absorption phase are often relatively limited to inform a more complex profile. To determine the absorption kinetics, one may examine the plot of logarithmic concentration *versus* time for the population and make a decision from there, e.g., a first-order absorption model. This approach, however, may mask some misspecifications, and with the increased sampling frequency during absorption, the complexity of drug absorption becomes obvious and the misspecification could be seen from the diagnostic plots. Sometimes it might initially seem that a simple first-order absorption model is sufficient by inspecting the data, but, upon closer examination of the diagnostic plots, a more complicated absorption profile may be hidden. An inappropriate absorption model can result in the misspecification of the disposition model, as well as inflating the inter-individual variability and residual unexplained variability, risking an erroneous prediction of the dosage regimen. Therefore, it is essential to pay close attention to the absorption phase of the diagnostic plots and optimize the absorption model when characterizing the pharmacokinetics of oral drugs, particularly those with erratic absorption profiles. In practice, we commonly encounter perplexing absorption features in drugs with progressive dissolution along the gastrointestinal tract followed by subsequent intestinal absorption, gradual absorption delay, saturable absorption, enterohepatic recirculation, etc. More flexible empirical modeling strategies have been established to describe various atypical absorption profiles. This includes a simultaneous or a sequential combination of zero-order and first-order absorption,

transit compartment absorption as an alternative to the lag time model in describing absorption delay (Erlang distribution function [17] or estimation of an optimal number of transit compartments [18]), Weibull-type absorption, absorption window-type with or without Michaelis-Menton absorption, time-dependent absorption rate, and inverse Gaussian density input-function [18, 19].

### 1.5 Obesity

The prevalence of obesity (body mass index [BMI] ≥30 kg/m$^2$) nearly tripled over the past 50 years with 39% of the world's adult population classified as overweight (BMI ≥25 kg/m$^2$), and 13% classified as obese [20]. Obesity impacts not only patients' health, leading to a myriad of comorbidities, but also the management of these diseases [21]. Obese individuals were reported with an increased risk to develop infections, including fungal infections [22-24]. Worse clinical outcomes were observed in obese patients with candidemia compared with non-obese patients [25]. Altered gut permeability, gastric emptying, cardiac output, liver- and renal capacity were demonstrated in obese and particularly morbidly obese individuals, which may impact drug absorption, distribution, metabolism, and excretion, thereby altering the pharmacokinetic profiles for drugs in this population [26]. In practice, unlike other special populations including children (pediatrics), the elderly (geriatrics), and pregnancy (obstetrics), the obese are often left out of pre-marketing clinical trials by the regulations. As a result, therapeutic protocols for obese patients are often lacking.

Obesity is associated with underdosing in the majority of antimicrobials, which can potentially lead to prophylactic or treatment failure [24, 25, 27]. There are a few commonly accepted assumptions to *a priori* predict the impact of obesity on drug pharmacokinetics. Lean body weight has been considered the preferred descriptor of clearance for obese individuals, but it was demonstrated to not be justified because there is unfortunately no size descriptor that can predict clearance for all drugs, even though total body weight appears to be the primarily selected descriptor for clearance based on the hitherto published studies [28]. The volume of distribution is often assumed to be larger in the obese population for lipophilic drugs, but not for hydrophilic drugs. This assumption does not stand for all circumstances as the volume of distribution is often (slightly) larger for hydrophilic drugs, while a high inter-drug variability was reported for lipophilic drugs [28]. CYP3A4 activity is usually presumed to be suppressed, while UDP-glucuronosyltransferase (UGT) activity is presumed to be increased in obese individuals [28]. These two assumptions only consider changes in the activity or abundance of hepatic enzymes resulting from obesity-related changes, but ignore the change in plasma protein binding, hepatic blood flow, and drug extraction ratios and thus fail to be generalizable to all drugs. It is also believed that the glomerular filtration rate is higher in obese *versus* non-obese populations, due to an increased renal blood flow and increased number and/or efficiency of functional nephrons. However, this assumption does not take renal diseases, altered transporter-mediated secretion, or reabsorption into consideration,

therefore also failed to be generalized to all scenarios [28]. As listed above, quite some commonly accepted assumptions to a *priori* predict the impact of obesity on drug pharmacokinetics are not generally valid. Considering the high mortality of invasive fungal diseases, it is necessary to investigate the pharmacokinetic changes of the commonly used antifungal drugs in obese *versus* non-obese populations and to identify predictive covariates to guide dosing.

### 1.6 Aims and scope of this thesis

The principal aim of this thesis is to better understand the pharmacokinetics of two triazole antifungals, i.e., posaconazole (**Chapters 2-4**) and fluconazole (**Chapter 5**), with a special focus on oral absorption and bioavailability, and therefore to guide dosing that maximizes the antifungal efficacy. For the pharmacokinetic study of posaconazole, we first had a comprehensive overview of what is currently known regarding the pharmacokinetics and pharmacodynamics of posaconazole (**Chapter 2**). Second, we integrate hitherto the most massive data from posaconazole oral suspension, delayed-release tablet, and intravenous infusion, in healthy volunteers, to simultaneously quantify the pharmacokinetics and clarify the pharmacokinetic differences among all these currently available formulations (**Chapter 3**). Third, we extended this integrated pharmacokinetic analysis to (mainly) hematological patients with the purpose of quantifying the influence of clinical characteristics, including Chinese ethnicity, on the pharmacokinetics of posaconazole for three formulations (**Chapter 4**). Last, we aim to bridge the knowledge gap of the impact of obesity on the pharmacokinetics of fluconazole. Using this knowledge, we proposed guidance on optimized fluconazole dosing for this special population (**Chapter 5**).

The current section outlines the general knowledge of invasive fungal diseases and the populations vulnerable to these diseases, current antifungal treatment options and challenges, basic concepts in population pharmacokinetic modeling and simulation, the importance of oral drug absorption in pharmacokinetic analysis, and the prevalence of obesity along with the dosing challenges in this population. This section points out that population pharmacokinetics serves as a powerful tool that allows us to understand one drug's pharmacokinetics of various formulations and among various populations. It also emphasizes the importance of characterizing the absorption feature in investigating the pharmacokinetics of oral drugs, and the demand for attention in quantifying the pharmacokinetics in special populations, such as obese individuals.

Posaconazole, a second-generation triazole, is playing a major part in preventing or treating invasive aspergillosis and mucormycosis. In **Chapter 2,** we reviewed the currently available knowledge on posaconazole pharmacokinetics, pharmacodynamics, major toxicity, existing resistance, clinical experience in special populations, and new therapeutic strategies to get a clear understanding of the clinical use of this drug. Through the literature search, we found that there is a plethora of

pharmacokinetic information on posaconazole oral suspension, while new information on the pharmacokinetics of both the delayed-release tablet and the intravenous formulation is emerging rapidly. These studies are however predominantly performed in one, and at most two of the three marketed posaconazole formulations, which exposed a knowledge gap for an integrated analysis that quantifies and compares the pharmacokinetics of all three formulations in parallel.

To circumvent the potentially confounding influence of pathological and clinical factors, we conducted an integrated population pharmacokinetic analysis in **Chapter 3,** which pooled by far the largest data in only a healthy population from all three formulations of posaconazole. In this analysis, we explored various empirical absorption models to characterize the absorption profiles of oral suspension and delayed-release tablets. To better describe the nonlinear saturable bioavailability in the oral suspension based on prior knowledge, the data was enriched by the meta-data from the literature. With the quantified absolute bioavailability and absorption rate for both oral formulations, including food effects, this study provided a quantitative reference when facing the formulation trade-offs.

Yet, these findings cannot be directly extrapolated to patients as the physiological function in patients is often more variable compared with the healthy population. The concomitant medications and complications are expected to further perplex the pharmacokinetics in patients. Moreover, the Chinese population was reported with a 25% lower clearance compared to the other global population based on clinical trials, but this has not yet been evaluated in clinical practice. Therefore, in **Chapter 4**, we added pharmacokinetic data from patients covering posaconazole three formulations to the rich data from the healthy volunteers and conducted an integrated analysis to investigate the impact of clinical characteristics and Chinese ethnicity on the pharmacokinetics of posaconazole in patients. Using these analytical results, licensed posaconazole dosage regimens were evaluated in patients under various possible clinical scenarios to guide dosing.

In **Chapter** 5, we investigated the pharmacokinetics of another very frequently used antifungal agent within the triazole family, fluconazole, which is mainly used to prevent and treat Candida infections. Despite that fluconazole has been marketed for 35 years, a dedicated study on the exclusive impact of obesity on the pharmacokinetics of fluconazole is still lacking. It is crucial to bridge this knowledge gap, particularly considering the expanding worldwide obesity pandemic and the high mortality associated with treatment failure from invasive fungal diseases, as well as the fact that commonly accepted assumptions are not generally valid to predict the impact of obesity on drug pharmacokinetics. In this study, we performed a prospective study in morbidly obese adults in comparison to non-obese adults using a semi-simultaneous design of oral and iv administration, which allows for estimating an accurate bioavailability and identifying descriptors for the inter-individual variability in fluconazole pharmacokinetics. Based on these findings, a dosing table was proposed for clinicians to treat *Candida* infections in obese adults.

In **Chapter 6**, the main findings from the previous chapters are summarized and discussed. The clinical significance is addressed. Furthermore, this section also outlines promising future opportunities on how to further improve antifungal therapy.



## 1.7 Reference


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