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Population pharmacokinetics of isavuconazole in hematologic patients: implications for model-informed precision dosing

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ABSTRACT

Background: Isavuconazole is a broad-spectrum antifungal agent used for treating invasive fungal infections (IFIs). Its pharmacokinetics may be impacted in hematologic patients due to concomitant clinical and therapeutic factors potentially affecting drug exposure. The aim of this study was to develop a population pharmacokinetic (popPK) model of isavuconazole in adult hematologic patients to support model-informed precision dosing.
Materials and method: Prospective, non-controlled study performed in adult hematologic patients receiving isavuconazole for IFIs and followed up by a therapeutic drug monitoring (TDM) program. Isavuconazole plasma concentrations were quantified using an ultra-high-performance liquid chromatography (UPLC) with UV detector. A popPK model was developed using NONMEM v.7.5.0. Simulations were based on the final model to evaluate the differences across physiological variables with impact on drug exposure.
Results: A one-compartment model with first-order absorption and elimination described adequately 121 isavuconazole concentrations from 52 patients. Body surface area (BSA) and serum albumin (ALB) significantly influenced drug clearance. The final popPK model showed good precision, robustness, and predictive performance, supporting its use for individualized isavuconazole dosing in this population.
Conclusions: BSA and serum ALB were identified as covariates influencing isavuconazole clearance in adult hematologic patients. Further studies are needed to better characterize the absorption of isavuconazole and implications on dosage recommendations, especially for higher proposed doses.

1. Introduction

Invasive fungal infections (IFIs) have become increasingly challenging for hospitals, as the number of patients susceptible to these infections has dramatically increased, resulting in high morbidity and mortality rates (Afhami et al., 2024). Triazole antifungals have emerged as first-line drugs for prophylaxis and treatment of IFIs. Isavuconazole the latest triazole to be marketed, is the only one approved by both EMA and FDA for the treatment of both invasive aspergillosis and mucormycosis (Ellsworth and Ostrosky-Zeichner, 2020). Compared to other azoles, isavuconazole has a better safety profile, causing dose-dependent QTc shortening instead of prolongation. As a moderate CYP3A4 inhibitor, it also has fewer significant drug interactions than other triazoles (Bose et al., 2018; Darnaud et al., 2018; Ellsworth and Ostrosky-Zeichner, 2020; Li et al., 2018). Otherwise, isavuconazole exhibits pharmacokinetic characteristics that are clinically relevant, including linear kinetics, high oral bioavailability (~98 %), a long terminal half-life (~130 h), and extensive protein binding (>99 %). The drug is primarily metabolized hepatically via CYP3A4, which may contribute to interindividual variability and potential drug–drug interactions (Desai et al., 2016a).

Therapeutic drug monitoring (TDM) is a widely used tool to optimize the safety and efficacy of other antifungal triazoles such as itraconazole, voriconazole, and posaconazole (Peña-Lorenzo et al., 2022). However, considering the isavuconazole safety profile previously mentioned, together with the favorable pharmacokinetic (PK) characteristics

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pointed out in the VITAL and SECURE clinical trials showing a minimal intra- and inter-subject variability and narrow distributions of isavuconazole trough levels, initially it was not considered necessary to carry out the TDM of this drug to personalize the dose (Andes et al., 2018; Maertens et al., 2016; Marty et al., 2016).

Despite the findings, real-world practice has shown instances where isavuconazole concentrations fall outside the expected levels, without any clear explanation related to known PK factors, such as drug interactions or CYP3A4/5 polymorphisms (Darnaud et al., 2018). Subsequent studies in clinical practice have revealed unexpected drug levels in various patient groups, particularly in those undergoing renal replacement therapy, extracorporeal membrane oxygenation, or among obese patients, pediatric patients (<18 years), individuals with cystic fibrosis, and those with moderate liver failure (Andes et al., 2018; Ellsworth and Ostrosky-Zeichner, 2020; Kabulski and MacVane, 2018; Zhao et al., 2020; Zurl et al., 2020). In addition, recent studies have suggested that plasma concentrations of isavuconazole higher than 2 μg/ml may be necessary to achieve therapeutic efficacy, while levels over the range of 4.6–5.1 μg/ml have been associated with an increased risk of toxicity, highlighting the importance of therapeutic monitoring in these patients (Borman et al., 2020; Denning et al., 2016; Furfaro et al., 2019; Kosmidis et al., 2021). These findings suggest that data from clinical practice may differ significantly from those obtained during the drug-development phase, leading to the conclusion that TDM for isavuconazole may be warranted under specific circumstances (Andes et al., 2018; Darnaud et al., 2018).

Despite these findings, gaps remain in our understanding of isavuconazole use in certain patient groups. In particular, no specific studies have been reported in hematologic patients, a group that is frequently treated with this antifungal agent. Moreover, these patients are often exposed to intensive immunosuppressive therapies, chemotherapy, and hematopoietic stem cell transplantation, which can affect the drug's absorption, metabolism, and elimination, and thus, drug exposition. Therefore, a more detailed evaluation in this population is needed.

In clinical settings, particularly in vulnerable populations such as hematologic patients, drug concentration data are often obtained through sparse and opportunistic sampling. This limits the feasibility of applying traditional non-compartmental analysis (NCA), which requires rich and frequent sampling to accurately estimate pharmacokinetic parameters. In contrast, population pharmacokinetic (popPK) modeling allows for the integration of heterogeneous and sparse data across individuals, making it the preferred approach to characterize drug exposure and variability in real-world conditions.

The aim of this study was to develop a popPK model for isavuconazole in adult patients with hematologic diseases in order to describe isavuconazole exposition in this population and support model-informed precision dosing (MIPD) strategies to optimize therapeutic outcomes and improve individualized treatment in this high-risk population.

2. Materials and methods

2.1. Study design and population

This was a prospective non-controlled intervention study carried out at the Clinical Pharmacokinetics Unit of the Pharmacy Service at the University Hospital of Salamanca (Spain) as part of a TDM program. The study was conducted over a follow-up period of thirty-two months.

The study protocol was authorized by the Ethics Committee of Clinical Research of the University Hospital of Salamanca (CEIC number: PI2020/03/460), and all patients signed informed consent regarding their willingness to participate in the study.

Adult hematologic patients receiving oral and intravenous isavuconazole for IFI prophylaxis or treatment who had drug levels drawn for TDM, were included in the study. Concomitant medications were reviewed in all cases, and patients with documented drug-drug interactions known to significantly alter isavuconazole concentrations—such as potent CYP3A4 inhibitors or inducers—were excluded from the analysis to avoid confounding effects on pharmacokinetic modeling. All patients received isavuconazole according to the dosing regimen approved in the Summary of Product Characteristics. The drug was administered either orally or intravenously at a loading dose of 200 mg every 8 h for 48 h, followed by 200 mg once daily as a maintenance dose, administered 12–24 h after the last loading dose. Dose adjustments were made according to TDM. All drug levels were drawn as part of routine care, with the decision to perform TDM made by the care team.

The following information was recorded for each patient: gender, age, height, total body weight (TBW), body surface area (BSA) which was calculated as weight (kg)$^{0.425}$ * height (cm)$^{0.725}$ * 0.007184, body mass index (BMI) calculated as weight (kg)/height^2 (m^2), albumin (ALB), total proteins, total bilirubin, aspartate aminotransferase, alanine aminotransaminase, alkaline phosphatase, γ-glutamyl transferase, urate, creatinine, estimated glomerular filtration rate calculated with CKE-EPI in mL/min, C-reactive protein, hemoglobin, and absolute neutrophil counts.

2.2. TDM strategy

Sampling schedules varied according to patient setting and route of isavuconazole administration. For all patients, the exact times of drug administration and blood sampling were accurately recorded and incorporated into the pharmacokinetic model as real-time data. In hospitalized patients, up to three samples were generally obtained per dosing interval, commonly at 0.5, 2, and 24 h following intravenous administration, or at 2, 3.5, and 24 h after oral dosing. However, this schedule could not always be strictly maintained due to clinical workflow constraints. In contrast, outpatients provided a single pre-dose sample, collected at a variable time point prior to oral administration, based on logistical feasibility within routine TDM practice.

Blood samples were collected in EDTA tubes. Immediately after drawing, samples were centrifuged (3700 rpm for 3 min) and two plasma aliquots were collected into labelled polypropylene Eppendorf tubes and stored at −18 °C, up to a maximum of 3 months.

2.3. Isavuconazole determination

Isavuconazole pure drug substance was provided by Sigma-Aldrich® laboratory (St. Louis, MO, USA). HPLC grade acetonitrile was supplied by Thermo Fisher Scientific® (Waltham, Massachusetts, USA). Formic acid was purchased from Sigma-Aldrich® laboratory. Ultrapure water was obtained with a Wasserlab Automatic Plus System.

Plasma concentrations of isavuconazole were measured by reverse-phase ultra-performance liquid chromatography (UPLC) using a Luna Omega C18 column (1.6 μm; 2.1 mm x 50 mm, Phenomenex Company). The mobile phase used for the elution consisted of a 55/45 mixture of 0.5 % formic acid and acetonitrile; the flow rate was 0.5 ml/min, and the UV detector was set at 285 nm. Column temperature was set at 40 °C; the sample manager was operated at 20° C, and the sample injection was 10 μl in a full-loop model.

Before the chromatographic injection, the samples were treated with protein precipitation with acetonitrile and later centrifugation at 5000 rpm for 5 min. The extraction efficiency of the direct plasma deproteinization method, verified in previous studies in the laboratory, was 92, 97, 104 and 102 % at 0.25, 1.0, 5.0 and 12.5 μg/ml of isavuconazole, respectively against the water.

The method was adequately validated for specificity, linearity, precision, accuracy, carry over and stability according to FDA Guidance and EMA Guidelines on bioanalytical method validation (U.S. Food and Drug Administration, 2018; Smith, 2012). The calibration range of the assay was 0.25–15.0 μg/ml.

2.4. Population pharmacokinetic analysis

A nonlinear mixed-effects modeling approach was employed to developed the popPK model, utilizing the first-order conditional estimation (FOCE) method with interaction in NONMEM® version 7.5.0 (Icon Development Solutions, Ellicott City, MD, USA). Data visualization and statistical analyses, as well as the assessment and presentation of model and simulation outcomes, were conducted using R version 4.4.2 (Beal et al., 2020).

As well as in previous studies, the pharmacokinetics of isavuconazole was initially described using a one-compartment model, testing different absorption models previously reported in pharmacokinetic studies of isavuconazole, including Weibull and first-order absorption (Desai et al., 2016a; Kovanda et al., 2016; Shirae et al., 2023). Although isavuconazole was administered both orally and intravenously, plasma concentrations collected during treatment did not allow for the estimation of absolute or relative bioavailability, as no patient had paired IV and oral data with sufficient sampling. As a result, bioavailability was fixed, pharmacokinetic parameters were considered apparent, and absorption parameters were fixed to values previously reported in the literature. The model was parameterized in terms of apparent clearance (CL/F), apparent volume of distribution (V/F), and the first-order absorption rate constant (Ka). In the case of the Weibull absorption model, the parameters tested were the shape factor (which describes the curvature of the absorption profile) and the scale parameter (which determines the time to reach peak absorption). Only concentration data from patients receiving oral isavuconazole were used to characterize the absorption component of the model.

The inter-individual variability (IIV) of the estimated pharmacokinetic parameters was assumed to follow a log-normal distribution. Residual unexplained variability (RUV) was explored using proportional, additive, or combined (proportional and additive) error models. The extent of IIV and RUV was approximately expressed as a coefficient of variation.

After selecting the base model (both structural and stochastic), all the variables previously described in Section 2.1 (demographic, clinical, therapeutic, etc.) were considered in the initial covariate analysis. The selection process involved a preliminary screening based on physiological plausibility, visual exploration of graphical trends, and stepwise linear regression to assess the relationship between the inter-individual variability (IIV) of isavuconazole pharmacokinetic parameters and continuous covariates. For categorical covariates, an analysis of variance (ANOVA) was conducted. Covariates were considered potentially relevant for further evaluation in the pharmacokinetic model if they were physiologically plausible, adequately represented in the study population, statistically significant ($p < 0.05$), and showed a coefficient of determination ($r^2 > 0.10$) with an IIV parameter. These covariates were then tested individually using a stepwise covariate modeling approach in NONMEM.

Furthermore, time-dependent factors, such as variations in renal function, and changes in drug metabolism, were also analyzed in NONMEM. Model performance was assessed through the likelihood ratio test (forward selection: $p < 0.05$; backward elimination: $p < 0.01$), in addition to reductions in IIV and RUV. The selection criteria also included evaluating the precision and bias of pharmacokinetic parameter estimates, following established methodologies (Savic and Karlsson, 2009).

The performance of the developed popPK model was evaluated through goodness-of-fit plots, including scatterplots of observed versus population-predicted concentrations and observed versus individual-predicted concentrations, as well as a prediction-corrected visual predictive check (pcVPC) (Bergstrand et al., 2011; Ette and Williams, 2007; Nguyen et al., 2017). The pcVPC was applied as an internal evaluation method within the development dataset, displaying the 5th, 50th, and 95th percentiles of the observed concentration-time data alongside the corresponding model-predicted percentiles and their 95 % confidence intervals (CIs), computed across different time bins since the first dose. A total of 1000 replicates of the original dataset were generated to support pcVPC analysis.

To assess the accuracy and robustness of the final popPK model, a nonparametric bootstrap analysis was conducted using 1000 bootstrap replicates, generated by random resampling from the original dataset. This analyses was conducted in PsN toolkit version 4.9. (Lindbom et al., 2005). Model parameters were estimated for each replicate, and only those models that successfully converged were considered for further analysis. The median and 95 % CI of each parameter were derived from the distribution of bootstrap estimates, providing a measure of model stability and parameter precision.

Table 1
Patient baseline characteristics and study data.

Number of patients	52
Demographics	
Age [median in years (range)]	59 (19–89)
Gender [female (%)]	54.9
Total body weight [median in Kg (range)]	70 (45–150)
Body mass index [median in Kg/ m^2 (range)]	25.6 (17.6–50.9)
Body surface area [median in m^2 (range)]	1.79 (1.41–2.60)
Biochemical parameters [median (range)]	
Total bilirubin (mmol/L)	0.7 (0.2–22.7)
Aspartate-transaminase (IU/L)	45 (5–568)
Alanine-transaminase (IU/L)	39 (7–767)
Alkaline phosphatase (IU/L)	97 (32–327)
Gamma-glutamyltransferase (IU/L)	72 (8–565)
Creatinine clearance (mL/min)[a]	102,9 (19.2–146.0)
Albumin (mg/dL)	3.1 (2.0–4.3)
Total serum proteins (g/dL)	5.2 (3.5–7.3)

[a] calculated with CKE-EPI equation.

2.5. Model based simulations and model-informed precision dosing nomogram

Deterministic simulations of isavuconazole concentration-time profiles were performed using the final popPK. The objective was to assess the impact of the identified factors on the predicted exposure and/or response to the drug, as well as its potential clinical relevance. For each scenario, defined based on the variables in the final model, isavuconazole administration was simulated until steady state was reached.

To develop the isavuconazole MIPD nomogram, a grid-based simulation approach was applied to evaluate the interaction between the identified covariates influencing drug exposure and the minimum dose required to maintain plasma concentrations within the therapeutic range (2–5 mg/mL). A range of values for these covariates was selected based on their distribution in the studied population. Monte Carlo simulations were performed for each combination of covariate values, to estimate steady-state plasma concentrations under different dosing regimens. The results were visualized using a color-coded heatmap, where the intersection of covariate values indicated the recommended maintenance daily dose to achieve therapeutic concentrations.

3. Results

3.1. Patient characteristics

A total of 121 isavuconazole concentrations from 52 patients were included in the analysis. The baseline patient characteristics and study data are summarized in Table 1. One patient was excluded due to a documented interaction with clarithromycin (strong CYP3A4 inhibitor). A sample from a single patient was discarded because the isavuconazole concentration was below the validated calibration range.

Table 2
Isavuconazole population pharmacokinetic parameters.

Parameters	Final model estimate	RSE (%)	Shrinkage	Bootstrap (n = 1000)	
				Mean	95 % CI
CLpop (L/h)	3.83	8		3.81	3.32–4.31
BSA-CL/F	1.80	30		1.83	0.82–2.72
ALB-CL/F	−0.19	34		−0.18	−0.27 - −0.06
Vpop (L)	226	20		220	149–285
Ka	22.6#			22.6#	
IIVCL/F (CV, %)	20.61	22	7	19.17	12.04–27.50
RUVprop (CV,%)	7.16	16	17	6.84	4.50–8.65

ALB, albumin in g/dL; ALB-CL/F, magnitude of the effect of ALB on CL; BSA, Body surface area in m^2; BSA-CL/F, magnitude of the effect of BSA on CL; CI, confidence interval; CLpop, clearance of the typical subject (ALB=3.1 g/dL, BSA = 1.8 m^2); IIVCL/F, interindividual variability on clearance; Ka: absorption rate constant; RSE, residual standard error; RUVprop, proportional error of residual variability; Vpop, volume of distribution of the typical subject; #, parameter fixed.

3.2. Population pharmacokinetic model

The pharmacokinetics of isavuconazole was best described by a one-compartment model with first-order absorption and elimination. The absorption rate constant (Ka) was fixed at 22.6 h^{-1} based on previous literature values (Cojutti et al., 2021).

An alternative Weibull-type absorption model was also tested, incorporating a time-dependent absorption function with a maximum absorption rate constant of 0.86 h-1, a lag time parameter of 0.653 h, and a shape parameter of 4.57 (Desai et al., 2016b). However, this model did not improve the objective function value (OFV), resulting in an increase of 16.51 units compared to the first-order absorption model, indicating a statistically worse fit ($\Delta OFV > 3.84$, $p < 0.05$). Furthermore, goodness-of-fit diagnostics and pcVPCs did not indicate any improvement in the description of isavuconazole absorption or its pharmacokinetic variability. Given the worsening of the OFV and the lack of meaningful enhancement in model performance, the simpler first-order absorption model was retained as it provided a more parsimonious and adequate representation of isavuconazole pharmacokinetics.

Based on previous isavuconazole PK models, body size metrics were a priori evaluated on the CL/F of the drug. Among the anthropometric parameters assessed (BSA, TBW, BMI), BSA with an allometric scaling relationship $(BSA/1.8)^{1.8}$ yielded the highest degree of influence on isavuconazole clearance and was considered the base model for further covariate assessment.

In the covariate analysis conducted, serum ALB exhibited significant influence on CL/F (p-value < 0.01) and were incorporated into the final model. The inclusion of these covariates in the model reduced interindividual variability (IIV) on CL/F from an initial value of 31.1 % to 20.61 % (Table 2). The final isavuconazole CL/F model is described by the following equation:

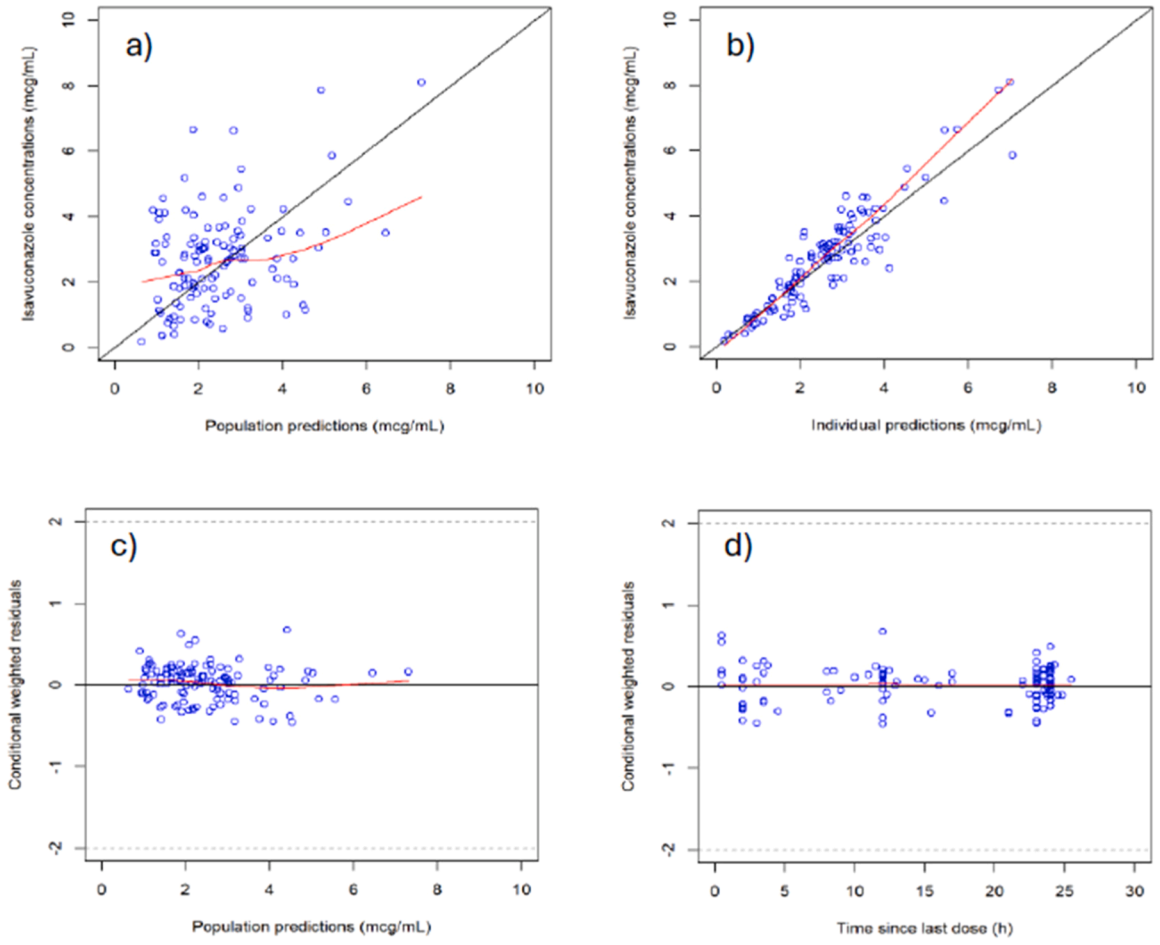

Fig. 1. Goodness-of-fit plots of the final model developed. (a) observed concentrations versus population predicted concentrations; (b) observed concentrations versus individual predicted concentrations; (c) conditional weighted residuals versus time; (d) conditional weighted residuals versus observed concentrations. Solid line: identity line; open circles: isavuconazole concentrations; red solid line: locally weighted scatterplot smoothing (LOWESS).

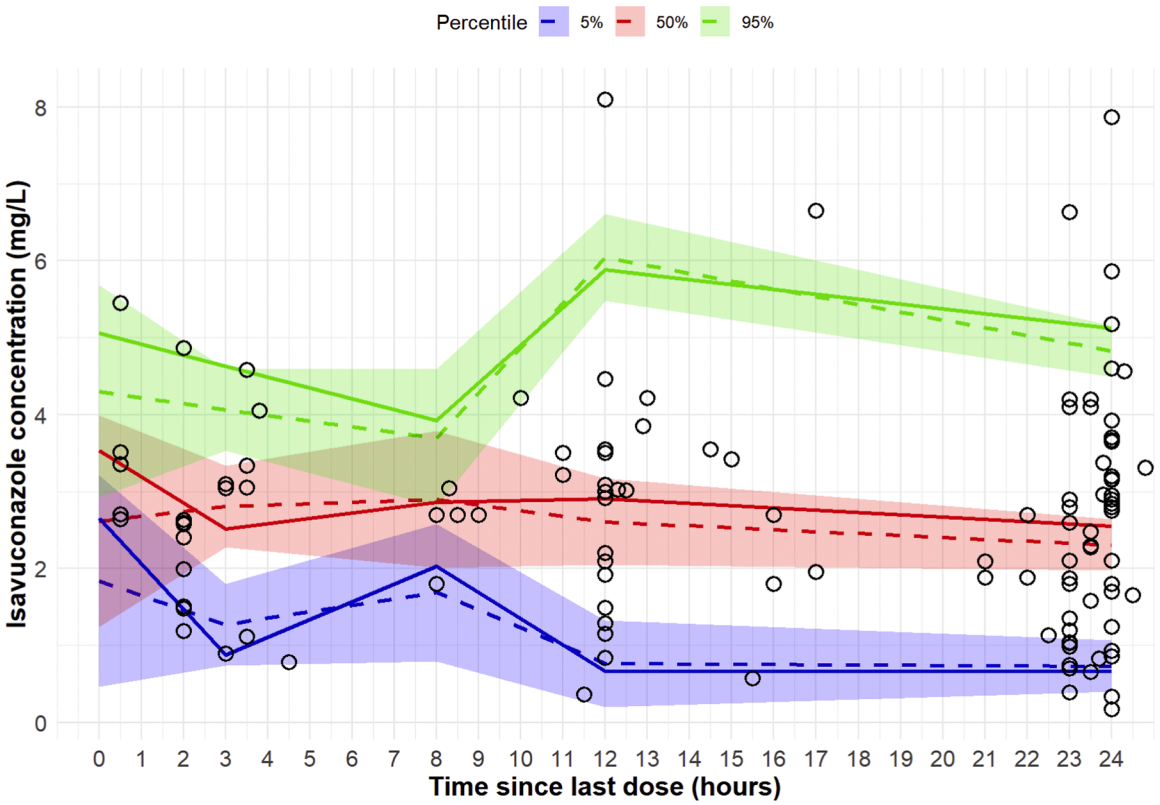

Fig. 2. Prediction-corrected visual predictive check (pcVPC) for the concentration-time after-dose profiles of isavuconazole in the studied population. The figure shows the empirical median and 5th and 95th empirical percentiles (solid lines), the theoretical median and the 5th and 95th theoretical percentiles (dashed lines), the 95 % confidence interval of the theoretical median and percentiles (shaded areas), and the observed isavuconazole concentrations (open circles).

$$\frac{CL}{F} = 3.83 \times \left(\frac{BSA}{1.8}\right)^{1.8} \times (1 - 0.19 \times (ALB - 3.1))$$

where isavuconazole CL/F, BSA, and ALB represent apparent clearance, body surface area, and serum albumin, expressed in L/h, m^2, and g/dL, respectively. Patients with missing albumin values were assigned a factor of 1, assuming no effect of ALB on CL/F in these cases. Graphical exploration did not reveal a differential effect of ALB at lower albumin levels, suggesting a linear relationship with CL/F across the observed range.

The V/F was estimated at 226 L, but its interindividual variability could not be estimated due to the limited data available. The RUV was 7.16 % (proportional error model).

3.3. Model evaluation

All pharmacokinetic parameters were estimated with adequate precision, as the relative standard error (RSE) was ≤ 35 % for all fixed-effect parameters. No systematic bias was observed, with shrinkage values ≤ 20 % for all parameters.

No significant differences were observed between the mean PK parameters obtained from the bootstrap analysis and the final PK parameter estimates. Additionally, all estimated parameters fell within the 95 % confidence intervals (CI) of the bootstrap results, supporting the robustness of the final model. None of the 1000 bootstrap runs were discarded due to boundary estimates, further demonstrating the stability of the model (Table 2).

Goodness-of-fit plots of the final popPK model showed a lack of structural bias and proper correlation between population and individual model-based predictions compared to the observed data (Fig. 1).

The pcVPC demonstrated an adequate description of the isavuconazole concentration-time course and its associated pharmacokinetic variability using the developed model (Fig. 2). Although individual concentration values and profile shapes are not directly interpretable due to the applied correction, this methodology, widely used in population pharmacokinetic models, further supports the reliability of the model in predicting isavuconazole pharmacokinetics.

4. Discussion

Therapeutic drug monitoring has been established as a key tool for optimizing the dosing of azole antifungals such as voriconazole, posaconazole, and itraconazole, allowing for treatment personalization, improved clinical outcomes, and minimized adverse effects (Peña-Lorenzo et al., 2022; Tissot et al., 2017; Ullmann et al., 2018). In particular, hematological patients exhibit pharmacokinetic alterations that may affect drug exposure, making TDM an essential strategy in this population (Laverdiere et al., 2014). While the need for TDM is well documented for other azoles, evidence regarding the clinical utility of isavuconazole TDM remains limited, highlighting the need for further studies to support its implementation in clinical practice.

The integration of popPK models within a Bayesian forecasting framework offers notable advantages for individualized dosing strategies. This approach enables the precise characterization of population-average PK parameters, as well as intra- and inter-individual variability, while identifying and quantifying key determinants of PK behavior. Despite these advantages, data on the pharmacokinetic behavior of isavuconazole in hematological patients remain scarce, and no specific population models have been developed to support TDM in this population. Therefore, access to robust and validated popPK models is essential for the successful implementation of an isavuconazole TDM program in routine clinical practice.

Expanding on this, we developed a popPK model based on data collected from 52 hematological patients treated with isavuconazole,

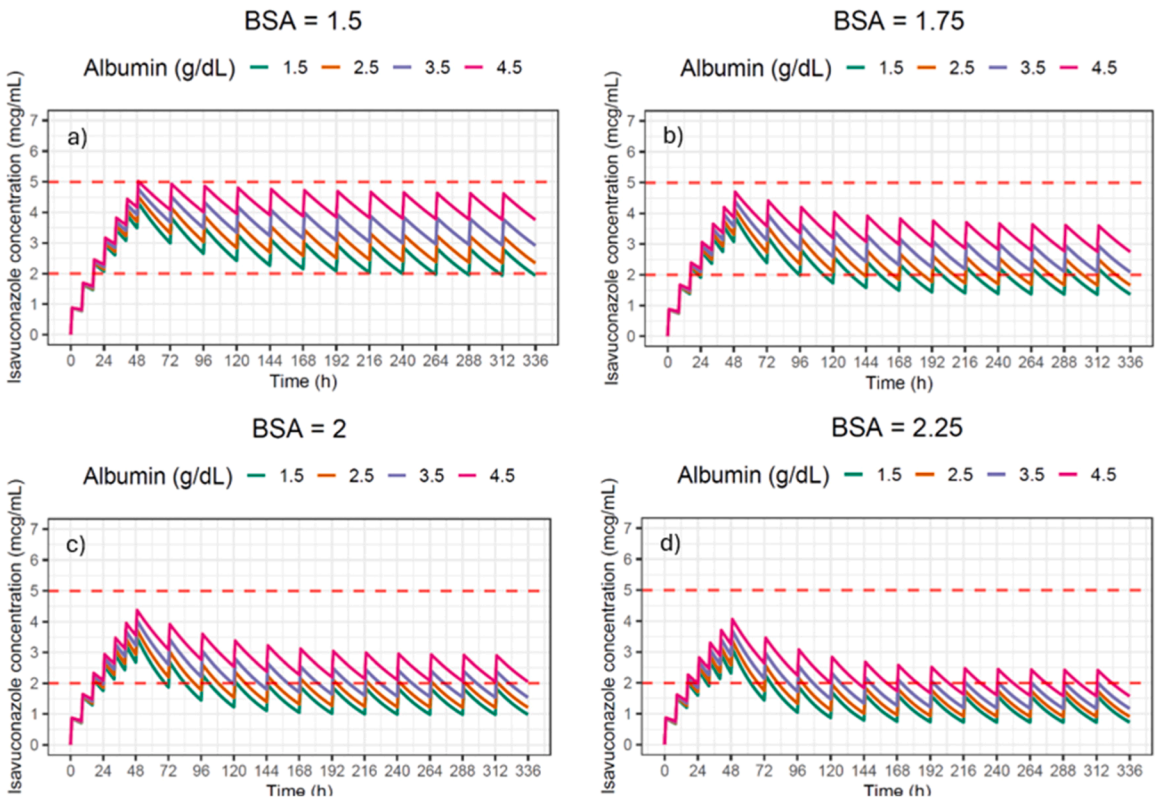

Fig. 3. Simulated time-concentration profiles of isavuconazole. Four panels corresponding to different BSA (m^2) values are presented: (a) 1.5, (b) 1.75, (c) 2, and (d) 2.25. Each panel illustrates the evolution of plasma concentrations for four albumin levels (1.5, 2.5, 3.5, and 4.5 g/dL) under a dosing regimen that includes a loading dose (6 doses of 200 mg every 8 h during the first 48 h) followed by a maintenance dose of 200 mg, simulated over 2 weeks of treatment. The red dashed lines indicate the lower (2 mg/mL) and upper (5 mg/mL) limits of the therapeutic range.

administered either orally or intravenously. In these patients the PK of isavuconazole in hematological patients was best described by a one-compartment model with first order absorption and elimination. Due to the limited availability of peak concentration data, the one-compartment model demonstrated higher parameter accuracy compared to a two-compartment model, which exhibited relatively lower accuracy in predicting peak concentrations.

It is important to note that since the efficacy and toxicity of isavuconazole appear to primarily depend on minimum concentrations, the maximum concentrations do not seem to pose a significant issue in this sense. This further supports the validity of the one-compartment model, which focuses on the key parameters affecting the drug's therapeutic profile, rather than emphasizing maximum concentrations which may be less clinically relevant in this case.

Additionally, we explored an alternative Weibull-type absorption model, which included a time-dependent absorption function. However, this model did not improve the objective function value compared to the first-order absorption model, leading to the retention of the simpler model. Although the Weibull model was tested, the limited availability of peak concentration data and the lack of significant improvement in the fit led to the decision to fix the Ka to the values previously reported by Cojutti et al. (2021), as this provided a more accurate and reliable representation of isavuconazole pharmacokinetics.

Model evaluation with goodness-of-fit plots, pcVPC, and bootstrap procedures demonstrated strong stability and reliable predictive performance of the final popPK model. Although increased variability in isavuconazole concentrations was observed at 12 h post-dose, the pcVPC showed that the model adequately captured both the median and variability at that time point. Most of these samples came from patients receiving individualized 12 h dosing regimens based on TDM. Therefore, the observed dispersion likely reflects true pharmacokinetic variability under non-standard conditions, rather than model misspecification, and does not compromise the predictive performance of the model.

The estimated population CL/F of isavuconazole was 3.83 L/h, which falls within the range reported in previous popPK studies in adult patients (1.52–4.28 L/h) (Cojutti et al., 2021; Desai et al., 2016a; Shirae et al., 2023; Wu et al., 2020). However, a direct comparison with CL/F values in hematological patients was not possible due to the lack of specific data in this population. In addition, the IIV on CL/F in our population was 20.61 %, substantially lower than the values reported in the literature (36.9 %−60.4 %) (Chen et al., 2023).

The estimated V/F was 226 L, which is relatively lower compared to some previously published models. However, comparing this value directly with other studies is challenging, as most of them employed a two-compartment model with Weibull absorption and first-order elimination, whereas our model used a one-compartment approach. The use of a two-compartment model can affect the estimated V/F, as it assumes a more complex distribution of the drug in the body with both central and peripheral compartments, which might result in a lower central volume of distribution compared to a simpler one-compartment model. This difference in modeling strategy, along with the specific characteristics of the hematologic patient population in our study, may explain the observed variation in V/F estimates.

Furthermore, the proportional RUV in our model was 7.16 %, which is also lower than previously reported values (17.4 %–36.1 %) (Chen et al., 2023). This low RUV, together with the reduced IIV on CL/F, supports the improved robustness and predictive precision of our model compared to earlier models.

The popPK model developed in this study evaluated the influence of various factors on isavuconazole exposure. Among them, ALB levels and BSA were identified as significant covariates affecting clearance. Isavuconazole CL/F increases as ALB levels decrease, potentially reducing

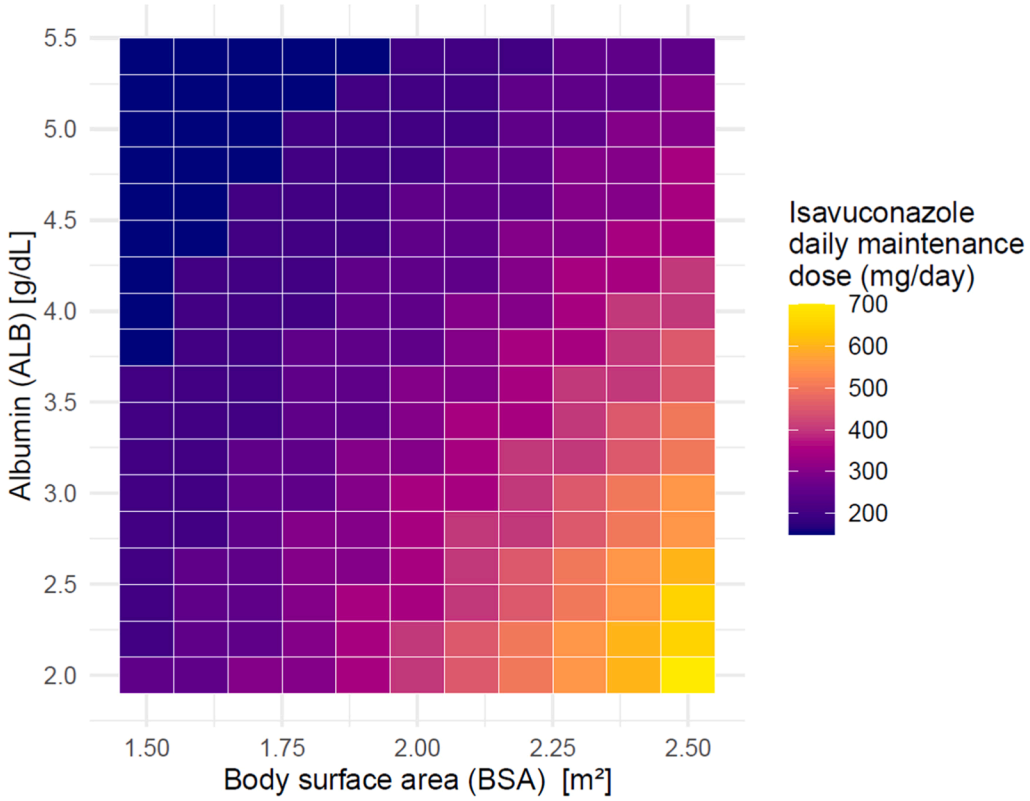

Fig. 4. Isavuconazole model-informed precision dosing nomogram. The figure illustrates the interaction between body surface area (BSA) and albumin (ALB) in determining the minimum dose required to maintain plasma concentrations within the therapeutic range (2–5 mg/mL). The intersection of these values, as indicated by the color scale in the legend, reveals the recommended maintenance daily dose of isavuconazole that ensures the therapeutic range is achieved.

total drug exposure while increasing free drug concentrations. Given that isavuconazole exhibits a high plasma protein binding rate (98–99 %), primarily to serum albumin, lower protein levels may lead to reduced binding and a higher proportion of free drug. Since only the free drug is available for distribution to tissues, including metabolic and excretory organs, protein binding plays a key role in isavuconazole elimination (Jansen et al., 2023; McCarthy et al., 2018).

In addition to ALB influence on isavuconazole elimination, BSA is a key determinant of clearance. Higher BSA is linked to increased metabolic capacity and blood flow to elimination organs, resulting in greater clearance. This observation aligns with allometric scaling principles, which relate clearance directly to body size (Anderson and Holford, 2008). Consequently, patients with higher BSA may require dosage adjustments to optimize therapeutic exposure. Moreover, other authors have identified lean body mass as an additional allometric parameter affecting isavuconazole elimination, underscoring the role of body composition in pharmacokinetic variability (Shirae et al., 2023).

These findings are especially relevant in hematologic patients, who frequently present with hypoalbuminemia due to systemic inflammation, chemotherapy-induced toxicity, or malnutrition (Lopez-Delgado et al., 2024; Soeters et al., 2019). Moreover, reduced BSA is commonly observed in elderly or cachectic patients, who make up a substantial proportion of this population (Macciò et al., 2015). These pathophysiological features may contribute to the observed variability in isavuconazole clearance, supporting the clinical relevance of incorporating ALB and BSA into individualized dosing strategies.

Since our results show that ALB and BSA appear to be important considerations for appropriate isavuconazole dosing, deterministic simulations were carried out to quantify the impact of these covariates on dose requirements.

As illustrated in Fig. 3, higher dose requirements have been described in patients with elevated BSA and in patients with hypoalbuminemia. Since dose escalation appears necessary in some patients, the nomogram proposed in Fig. 4 could be useful for selecting the maintenance dose of isavuconazole to avoid unnecessary underexposure.

Several population pharmacokinetic studies have identified race, sex, liver function, patient type, and creatinine clearance (CLcr) as significant covariates influencing isavuconazole clearance. For instance, CL/F has been reported to be approximately 36 % lower in Asian patients compared to Caucasians (Desai et al., 2016a), lower in elderly women than in men (Desai et al., 2019), and reduced in patients with mild-to-moderate hepatic impairment (Desai et al., 2016a). Additionally, CL has been found to be lower in patients compared to healthy volunteers (Shirae et al., 2023) and to increase slightly with higher CLcr (Shirae et al., 2023). However, our population consisted exclusively of Caucasian patients and no healthy volunteers, so these covariates could not be assessed.

In our study, neither sex, renal function, nor hepatic function significantly influenced isavuconazole clearance, suggesting that dose adjustments based on these variables may not be necessary in this specific population. However, future research in more diverse populations could help confirm these findings and further evaluate other potential determinants of the drug's pharmacokinetic variability.

On the other hand, although our study did not evaluate the potential impact of genetic polymorphisms on isavuconazole exposure or its interactions with CYP3A4/5 inhibitors or inducers, it is relevant to consider that, as a substrate of this isoenzyme, these drugs could theoretically influence its pharmacokinetic parameters through drug-drug interactions. However, in the population pharmacokinetic studies conducted by Desai et al. (2016a), Shirae et al. (2023), the effect of CYP3A4/5 inhibitors was not included as a covariate in the final models, suggesting that their clinical impact may be limited. These findings support the idea that, despite the pharmacological basis for such

interactions, their practical relevance in isavuconazole exposure may not be significant.

This study has some limitations. First, the sample size was small and, as previously mentioned, the analysis mainly involved trough concentrations, which was not sufficiently informative to adequately characterize the absorption phase in the studied population and made it necessary to fix the absorption parameters to previous reported values. Although some hospitalized patients contributed samples during the absorption window (e.g., at 2 or 3.5 h post-dose), the overall sampling density in this phase was limited, particularly among outpatients. A Weibull absorption model was explored but did not improve model performance, likely due to this sparsity. Future studies could benefit from targeted sampling in the early post-dose period or from leveraging external data or informative priors to support absorption parameter estimation. Secondly, due to the lack of additional patients, an external evaluation of the model could not be performed. This would have been particularly valuable for confirming the absorption model assumed in the final popPK model.

This study presents several strengths. The popPK model proposed was performed with real-world patients rather than in a clinical trial framework, which adds valuable information regarding isavuconazole PK in the clinical routine setting. The developed popPK model adequately described isavuconazole concentrations in hematologic patients, a population not previously studied in this context. To our knowledge, this is the first study conducted in hematologic patients. Furthermore, the main findings of this study are the factors identified as having a significant impact on isavuconazole pharmacokinetics, leading to the proposal of a nomogram based on PK/PD criteria. Indeed, the proposed isavuconazole popPK model should be considered for MIPD of this drug in adult hematologic populations.

5. Conclusions

In conclusion, the population pharmacokinetic model developed adequately characterized the pharmacokinetics of isavuconazole in hematologic patients following oral and intravenous administration. ALB and BSA were identified as covariates influencing isavuconazole CL/F in adult hematologic patients. Additional studies are required to better characterize the absorption of isavuconazole in the studied population, as well as its implications on drug elimination and dosing recommendations for the higher isavuconazole doses proposed.

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CRediT authorship contribution statement

Diego Peña-Lorenzo: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **José Germán Sánchez-Hernández:** Writing – review & editing, Software, Methodology, Data curation, Conceptualization. **Irene Conde-González:** Investigation, Data curation. **Aránzazu Zarzuelo-Castañeda:** Writing – review & editing, Validation, Methodology, Investigation. **Noemí Rebollo:** Writing – review & editing, Methodology, Formal analysis. **Lourdes Vázquez-López:** Supervision. **María José Otero:** Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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Data availability

The data that has been used is confidential.

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