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# Repurposing antifungals: population pharmacokinetics of itraconazole and hydroxy-itraconazole following administration of a nanocrystal formulation

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**Objectives:** To describe itraconazole and hydroxy-itraconazole pharmacokinetics following intravenous (IV) administration of a previously developed nanocrystal formulation (NCF) in haematopoietic cell transplant (HCT) recipients for prophylaxis of invasive fungal disease.

**Methods:** In a prospective Phase II study, 10 HCT recipients received itraconazole NCF administered in 2-hour infusions of 200 mg twice daily for 2 days, followed by 200 mg once daily until Day 14. Full pharmacokinetic curves were obtained on Days 7 and 14. Additional samples were collected pre- and post-infusion until Day 6, pre-infusion on Days 10 and 12, and during washout on Days 16, 17, 18, 19 and 28. Itraconazole and hydroxy-itraconazole pharmacokinetics were analysed by non-linear mixed-effects population pharmacokinetic modelling.

**Results:** Four-hundred and seventy-one itraconazole and 471 paired hydroxy-itraconazole concentrations from 10 patients were included for analysis. Data were best described by a semi-mechanistic model with central and peripheral itraconazole compartments and a hydroxy-itraconazole compartment with dissolution of itraconazole drug particles from nanocrystals and first-order distribution and elimination. The final model included interindividual variability on itraconazole clearance and hydroxy-itraconazole clearance.

**Conclusions:** This study provides information on the pharmacokinetic properties of the itraconazole NCF useful for development of this formulation. Our results suggest that itraconazole NCF is a suitable formulation and may warrant renewal in the setting of repurposing. Our findings may be useful for the reformulation of other highly lipophilic compounds as well.

## Introduction

Itraconazole is a broad-spectrum antifungal agent with activity against numerous medically relevant fungi and yeasts, among which are *Aspergillus* and *Candida* species.[1] Itraconazole is on the WHO Model List of Essential Medicines for the treatment of various fungal infections including chronic pulmonary aspergillosis and histoplasmosis.[2] Additionally, it is indicated for the prophylaxis of invasive fungal disease (IFD) in immunocompromised patients, including haematopoietic cell transplant (HCT) recipients.[3,4]

Itraconazole pharmacokinetics following oral administration are poor, highly variable and influenced by food intake while intravenous (IV) itraconazole formulations are not widely available.[5,6] To overcome these shortcomings, new pharmaceutical formulations have been developed, such as the oral super bioavailability (SUBA)-itraconazole formulation and an IV nanocrystal formulation (NCF).

Using a nanosizing technique, the water-based solution pluronic F108 is milled to formulate the highly lipophilic itraconazole as nanometer-sized drug particles creating a physically stable dispersion.[7] This process offers the opportunity to formulate drugs that are poorly water soluble without the need to add excessive amounts of co-solvents that could potentially cause undesirable side effects.[7]

Pharmaceutical development of a novel formulation warrants information on its pharmacokinetics. For the current IV formulation, interindividual variability (IIV) on itraconazole clearance was

reported to be 66% in patients with neutropenic fever.[8] The pharmacokinetic properties of the novel NCF may differ from this IV formulation, for example by the release of the itraconazole drug particles from the nanocrystals.[7,9]

Currently, only limited information on the pharmacokinetics of itraconazole administered as NCF in healthy subjects is available.[9] Yet, additional data are highly interesting in the setting of drug repurposing, given that such a formulation would allow wide access to an IV treatment option. We here describe the population pharmacokinetics of itraconazole and its pharmacologically active metabolite hydroxy-itraconazole and the associated variability after administration of itraconazole NCF in allogeneic HCT recipients.

## Methods

### Patients

This prospective, open-label Phase II study was conducted at the Department of Haematology at Radboudumc in patients receiving a matched allogeneic bone marrow transplant following conditioning with idarubicin, cyclophosphamide and total body irradiation. Patients were eligible for inclusion if they were between 18 and 65 years of age and had no signs or symptoms of fungal infection. Exclusion criteria were administration of any systemic antifungal therapy within the 2 weeks prior to inclusion, administration of co-medication with clinically relevant pharmacokinetic interaction with itraconazole within the 2 weeks prior to inclusion or at inclusion, liver enzyme values exceeding five times the upper limit of normal or bilirubin above 50 mg/L at inclusion, hypersensitivity for any (tri)azole antifungal agent, administration of another investigational drug in the month prior to inclusion, and previous inclusion in this study. Patients underwent routine observations including evaluation of QTc intervals upon entry in the hospital.

Subjects started 6 days before allogeneic bone marrow transplant with itraconazole prophylaxis. Itraconazole was administered as IV NCF in 2-hour infusions of 200 mg twice daily for 2 days, followed by 200 mg once daily until Day 14 based on the multiple ascending dose study in healthy volunteers.[9] Administration of itraconazole NCF was started after completion of induction chemotherapy. Trial medication was provided by the Janssen Research Foundation. If itraconazole NCF administration was stopped before completing the 14 day course, subjects were considered dropouts and were replaced. Any data collected before dropout would be included in the analyses.

Relevant patient characteristics including age, sex, weight and height were assessed at baseline. Vital signs and any adverse events were recorded at baseline and hourly during 4 h after each infusion. Laboratory safety parameters were assessed at baseline and Days 2, 3, 5, 7, 14 and 28. Identification of potentially relevant covariates was not part of this Phase II study.

### Pharmacokinetic sampling and assay

Blood samples were collected pre-dose ($t=0$) and after infusion ($t=2$) for all administrations until Day 6 of itraconazole prophylaxis. On Days 7 and 14, full pharmacokinetic curves were obtained by sampling at $t=0$, 0.25, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h after start of infusion. Additional samples were collected pre-infusion on Days 10 and 12, and once per day during the washout period on Days 16, 17, 18, 19 and 28 after treatment initiation. As described earlier, blood samples were left undisturbed after collection for at least 2 hours at room temperature to assure the complete dissolution of the itraconazole from the NCF and minimal bioanalytical variability.[9] Blood samples were then centrifuged for 10 min at 1000 **g** to obtain plasma. Itraconazole and hydroxy-itraconazole concentrations in plasma were quantified using an HPLC assay.[10] The lower limits of quantification (LLOQs) for itraconazole and hydroxy-itraconazole were 0.002 and 0.005 mg/L, respectively. The accuracy ranges were 97.1%–98.7% and 94.7%–99.5% for itraconazole and hydroxy-itraconazole concentrations, respectively. The precision (coefficients of variation) ranges for itraconazole and hydroxy-itraconazole concentrations were 1.0%–3.4% and 1.4%–3.1%, respectively. All samples were analysed immediately after the end of the clinical trial. The study was conducted earlier but could not be published at the time because of a dispute about intellectual property. However, this matter was resolved, allowing us to analyse and publish these data (R. J. M. Brüggemann, Radboud University Medical Center, personal communication).

### Population pharmacokinetic analysis

Itraconazole and hydroxy-itraconazole pharmacokinetics were analysed by means of non-linear mixed-effects modelling using NONMEM® (version 7.4.1) with Pirana (version 2.9.7) as interface for Perl-Speaks-NONMEM, Xpose and R statistics.[11]

All itraconazole and hydroxy-itraconazole plasma concentrations were converted to molar equivalents to account for differences in mass. Subsequently, data were log-transformed because of wide ranges in observed concentrations, which were all above the LLOQ. Model development was conducted in a stepwise manner. First, only itraconazole data were used to develop a base model, which was later extended with hydroxy-itraconazole data. One-, two- and three-compartment models were considered. In the absence of metabolic conversion data and in the knowledge that the percentage of itraconazole that is excreted unchanged is very small, the fraction of itraconazole metabolised to hydroxy-itraconazole was assumed to be 1, in line with previous population pharmacokinetic studies.[12,13]

Parameters were *a priori* allometrically scaled to a total body weight of 70 kg with a fixed exponent of ¾ for (intercompartmental) clearance, and 1 for volumes of distribution.[14] IIV was assumed to be log-normally distributed. To model the residual variability, constant as well as proportional and combined constant and proportional models were evaluated for both the parent and metabolite compound data together and separately.

To describe the dissolution of itraconazole drug particles from the nanocrystals, a dissolution rate constant was fixed between a nanocrystal-bound itraconazole compartment, where doses were administered, and the central itraconazole compartment, where itraconazole concentrations were observed. The rate of dissolution from the nanocrystals ($k_N$) was fixed at 4.62 $h^{-1}$ based on a dissolution half-life of 9 min in human plasma.[9] The volume of distribution for nanocrystal bound itraconazole ($V_N$) was assumed to be equal to the volume of distribution of the central itraconazole compartment. Observed itraconazole concentrations were fitted under the assumption that they were the sum of nanocrystal-bound and nanocrystal-unbound itraconazole concentrations.

Throughout the analysis, the first-order conditional estimation (FOCE) method was used to fit models, with the interaction option for models with a proportional residual error model. Structural model development was based on physiological plausibility, diagnostic goodness-of-fit plots, a successful covariance step, and parameter correlation assessment. Additionally, nested models were statistically compared using the change in objective function value (OFV). A decrease in OFV of at least 3.84 for chi-squared distribution with one degree of freedom for a significance level of $P<0.05$ relative to the comparative model was considered superior. Non-nested models were compared using the Akaike information criterion (AIC). Models with lower AIC were considered superior. Parameter uncertainty was assessed by sampling importance resampling (SIR).[15]

The final population pharmacokinetic model was used to simulate itraconazole and hydroxy-itraconazole trough concentrations ($C_{min}$) at steady state in patients receiving the standard itraconazole dose of 200 mg itraconazole as NCF once per day. Monte Carlo simulations

were performed based on a real-life database from our haematology department with demographic data of 1576 haematology patients. Findings were compared with the itraconazole target $C_{min}$ of >0.5 mg/L and >1.0 mg/L, and with itraconazole plus hydroxy-itraconazole target $C_{min}$ of >1.0 mg/L and >2.0 mg/L for prophylaxis and treatment, respectively.[4,16] Additionally, findings were compared with the itraconazole $C_{min}$ of <4.0 mg/L associated with toxicity.[17]

### Ethics

This study was conducted according to the ethical guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Radboud University Medical Center, Nijmegen, The Netherlands (reference number CWOM 9811-0246). Written informed consent was obtained from all participants before study inclusion.

## Results

Ten patients were included in the study, allowing analysis of 471 itraconazole and 471 paired hydroxy-itraconazole plasma concentrations. Baseline patient characteristics are detailed in Table 1. All patients received 14 days of itraconazole NCF and were sampled until Day 28. Overall, itraconazole NCF was well tolerated. No serious adverse events were reported; 8 out of 10 patients experienced mild to moderate adverse events potentially related to the itraconazole NCF administration: dizziness ($n=4$), headache ($n=3$), hypertension ($n=3$), hypotension ($n=2$), vomiting ($n=3$), nausea ($n=2$), hiccoughs ($n=1$), lethargy ($n=1$), tachycardia ($n=1$). All patients recovered from these adverse events. No breakthrough infections were reported in the studied population.

Itraconazole and hydroxy-itraconazole concentrations in the dataset ranged from 0.06 to 6.96 mg/L and from 0.09 to 1.86 mg/L, respectively. Mean (SD) $C_{min}$ at steady state (after Day 7) were 0.79 mg/L (0.35) and 1.31 mg/L (0.29) for itraconazole and hydroxy-itraconazole, respectively. The observed itraconazole and hydroxy-itraconazole $C_{min}$ over time are presented in Figure S1 (available as Supplementary data at *JAC* Online).

Itraconazole and hydroxy-itraconazole pharmacokinetics following IV administration of the NCF were best described by a semi-mechanistic model consisting of a central and peripheral itraconazole compartment with an additional compartment for nanocrystal-bound itraconazole drug particles and one hydroxy-itraconazole compartment with first-order elimination. The final model included IIV on itraconazole clearance and hydroxy-itraconazole clearance. The residual variability was best described by an additive residual error model on the log scale, corresponding to proportional error models for both the parent and metabolite compound separately. The model improved significantly after addition of correlation between the itraconazole and hydroxy-itraconazole proportional residual variability. The final model is schematically presented in Figure S2 and the final model control stream is available as Supplementary data. Table 2 summarizes the population parameter estimates of the final model with confidence intervals (CI) representing the uncertainty around the model parameter estimations as assessed by SIR. All hydroxy-itraconazole parameters are apparent to the fraction metabolised.

In general, the observed data were adequately described by the final model, as illustrated in the general goodness-of-fit plots and, even more so, in the prediction-corrected visual predictive check plots in Figures S3 and S4, respectively. For the itraconazole data, unexplained variability remained in the current model, as indicated by the wider spread of observations around the line

**Table 1.** Baseline patient characteristics of the study population

| Characteristics | Values |
|---|---|
| Total number of patients, *N* | 10 |
| Age (years), median (range) | 47.5 (22.0–59.0) |
| Sex, female, *n* (%) | 5 (50) |
| Weight (kg), median (range) | 78.3 (60.0–92.5) |
| Height (cm), median (range) | 172 (164–190) |
| BMI (kg/m$^2$), median (range) | 25.3 (20.6–29.4) |
| Underlying disease, *n* (%) | |
| ALL | 3 (30) |
| AML | 2 (20) |
| CML | 2 (20) |
| NHL | 2 (20) |
| Myelofibrosis | 1 (10) |

BMI, body mass index; ALL, acute lymphatic leukaemia; AML, acute myeloid leukaemia; CML, chronic myelomonocytic leukaemia; NHL, non-hodgkin lymphoma.

**Table 2.** Population pharmacokinetic parameter estimates of the final model

| Parameter | Population estimate | 95% CI[a] |
|---|---|---|
| $CL_P$ (L/h) | 4.29 | 3.85–4.80 |
| $V_{P1}/V_N$ (L) | 14.1 | 11.8–17.2 |
| $Q_P$ (L/h) | 53.0 | 45.3–63.4 |
| $V_{P2}$ (L) | 1660 | 1558–1775 |
| $CL_M$ (L/h) | 2.86 | 2.43–3.33 |
| $V_M$ (L) | 43.1 | 36.9–50.4 |
| IIV[b,c] | | |
| IIV $CL_P$ (%) | 11.3 | 5.2–19.0 |
| IIV $CL_M$ (%) | 22.8 | 15.4–34.5 |
| Residual variability[b,c] | | |
| $Error_P$ (%) | 48.8 | 45.7–52.8 |
| $Error_M$ (%) | 19.1 | 18.0–20.5 |
| Correlation $error_P$, $error_M$ (%) | 48.5 | 34.7–56.6 |

CI, confidence interval; $CL_M$, hydroxy-itraconazole clearance; $CL_P$, itraconazole clearance; $Q_P$, itraconazole intercompartmental clearance; IIV, interindividual variability; RSE, relative standard error; $V_M$, hydroxy-itraconazole central volume of distribution; $V_N$, nanocrystal-bound itraconazole volume of distribution; $V_{P1}$, itraconazole central volume of distribution; $V_{P2}$, itraconazole peripheral volume of distribution.
[a]Parameter precision obtained by the SIR procedure using 2000 samples and 1000 resamples.
[b]Transformed from log-normal variance to %CV with $\sqrt{(e^{\omega^2}-1)}$.
[c]Eta and epsilon shrinkage all below 15%.

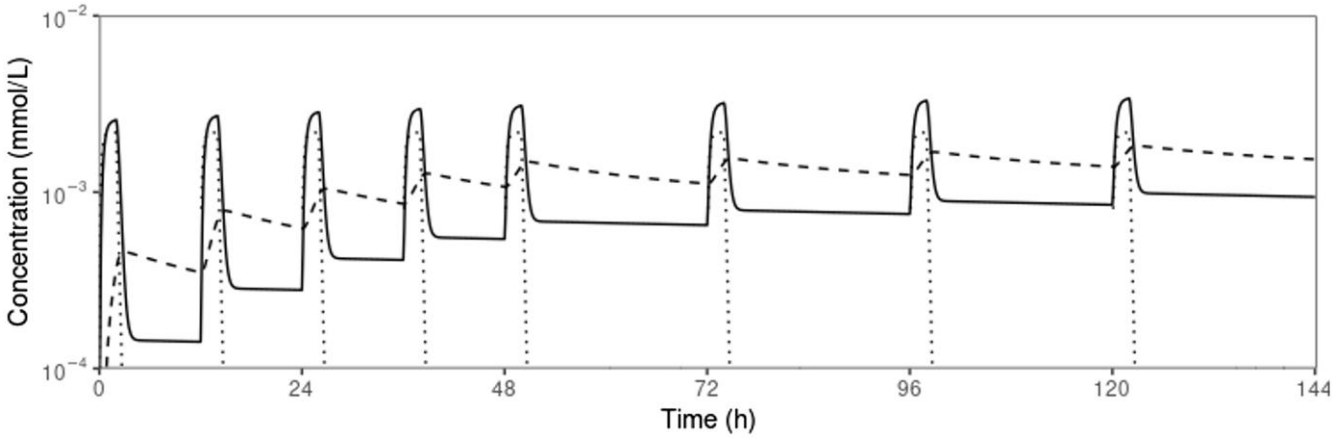


**Figure 1.** Simulated nanocrystal-bound itraconazole (dotted line), itraconazole (solid line), and hydroxy-itraconazole (dashed line) concentration–time profiles for a typical individual following itraconazole NCF administrations according to study protocol for 7 days.

of unity, mainly at higher concentrations. The homogeneously distributed conditional weighted residuals (CWRES) over time and predicted concentrations indicate that there is no major model misspecification for both the itraconazole and hydroxy-itraconazole data. The average CWRES for itraconazole and hydroxy-itraconazole data were 0.00065 and −0.00040, respectively. The few observations outside the desired −2 to 2 CWRES range were particularly seen at low observed hydroxy-itraconazole concentrations, although above the LLOQ, possibly owing to the late timepoints exceeding 300 hours after last dose.

The simulated nanocrystal-bound itraconazole, itraconazole and hydroxy-itraconazole concentration–time curves for a typical individual, based on simulations using the final model and itraconazole NCF dosing as per protocol, are presented in Figure 1. The simulated $C_{min}$ at steady state are shown in Figure S5. In patients receiving the standard dose of itraconazole as NCF, all reached the predefined itraconazole and itraconazole plus hydroxy-itraconazole target $C_{min}$ for prophylaxis. The predefined itraconazole and itraconazole plus hydroxy-itraconazole target $C_{min}$ for treatment were reached in 54.4% and 91.8% of patients, respectively. None of the itraconazole $C_{min}$ exceeded the target $C_{min}$ of 4.0 mg/L associated with toxicity.

## Discussion

With this study, we describe the population pharmacokinetics of itraconazole and its pharmacologically active metabolite hydroxy-itraconazole following IV administration of itraconazole as NCF in allogeneic HCT recipients. This study thereby provides useful information on the pharmacokinetic properties needed for development of this itraconazole formulation.

The current formulation is not further developed, yet it may still provide a valuable addition to our current antifungal armamentarium as itraconazole remains an important treatment option for certain fungal infections, such as chronic pulmonary aspergillosis and histoplasmosis. This is underlined by the WHO, that listed itraconazole among the most efficacious, safe and cost-effective medicines for a basic healthcare system on their Model List of Essential Medicines.[2] A recent report on the global consumption of antifungal agents in humans shows that in the last decade the use of itraconazole has increased in middle-income countries.[18] Further development of this novel NCF may be valuable for those patients requiring IV treatment, although large-scale production could be challenging.

To date, only limited pharmacokinetic information on the itraconazole NCF is available from a non-compartmental analysis in a group of healthy volunteers.[9] Here, four healthy subjects received multiple doses of 200 mg itraconazole as NCF. The reported mean (SD) steady-state $C_{min}$ values were 1.25 mg/L (0.34) and 1.79 mg/L (0.21) for itraconazole and hydroxy-itraconazole, respectively. Mean steady-state $C_{min}$ values in the current study were lower for both parent and metabolite, but well above the target levels for therapeutic drug monitoring.[16] Differences may be explained by the small sample size and the differences in pharmacokinetics that can be expected between healthy volunteers and patients.

Looking into the population pharmacokinetics of IV-administered itraconazole, there is only one study by Lee *et al.*[8] describing a pharmacometric analysis of itraconazole after IV administration of a parenteral formulation with hydroxypropyl-beta-cyclodextrin (HPBCD) as co-solvent. While this model structurally differs from ours as it only describes one itraconazole compartment, this is most likely driven by the sparseness of their data. Other models describing itraconazole pharmacokinetics after oral administration identified two compartments for the parent drug as well.[12,13,19] Furthermore, the model by Lee *et al.* assumes half of itraconazole is metabolised to hydroxy-itraconazole and the other half is excreted unchanged. However, the unchanged fraction of itraconazole is reported to vary between 3% and 18% of the given dose.[20] When it is not possible to estimate the metabolic ratio in the absence of data on IV-administered metabolite, it seems more appropriate to assume all instead of half of itraconazole is metabolised to hydroxy-itraconazole, as done in the current study and previous population pharmacokinetic studies on oral itraconazole as well.[12,13] The itraconazole volume of distribution found in the current study was larger compared with the 1050 L that Lee *et al.* reported. The large volume of distribution of itraconazole is

chiefly attributable to the lipophilicity of the compound, and the increase seen in the current study may possibly be explained by trapping of nanometer-sized drug particles in the Kupffer cells, as indicated in animal studies.[7,9] Due to the differences in parametrization, other final parameter estimates could not be compared with our findings.

In the absence of nanocrystal-bound itraconazole concentrations, the current model assumes $V_N$ is equal to the volume of the central itraconazole compartment, although it may be argued whether this is correct. It should also be noted that the current model was developed based on data from a small group of patients and without a formal sample size calculation. Despite the very rich sampling, the sample size of this study did not allow us to include more IIV and intra-individual variability in the model without introducing an increase in model misspecification. Our study was not powered to identify any covariates accounting for itraconazole pharmacokinetic variability, leaving out some unexplained variability in the current model. Nevertheless, in general, population pharmacokinetic modelling is well suitable for small sample sizes and sparse data.

Given the wide pharmacokinetic variability for oral itraconazole,[21,22] it may be preferred to initiate IV treatment for high-risk patients as it assures more reliable bioavailability. In some cases, oral intake of drugs may not be possible at all, such as for patients who heavily vomit or those who suffer from severe mucositis or graft-versus-host disease (GvHD). Findings of the current study show that adequate itraconazole and hydroxy-itraconazole $C_{min}$ can be obtained with the NCF,[16] making it a viable alternative to the existing formulation for further optimization of antifungal therapy.

Repurposing of drugs to enhance usage has gained increased interest in the field of antifungal therapy, with the development of liposomal amphotericin B and, more recently, the SUBA-itraconazole formulation.[13,23] Also beyond this scope, there are many drugs with suboptimal bioavailability and there is a need for formulating options in case of poor water solubility. Therefore, the findings of this study may be of interest to researchers and clinicians of various therapeutic fields.

In conclusion, with this study we provided information on the pharmacokinetics of itraconazole and hydroxy-itraconazole in HCT recipients following administration of itraconazole NCF, which could be useful in the dose development of this formulation. Our results may give rise to the renewal of the IV itraconazole formulation in the setting of drug repurposing. Additionally, findings on the pharmacokinetics of the NCF in this study may be useful for reformulation of other highly lipophilic compounds as well.

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## Transparency declarations

None to declare.

### *Author contributions*

J.P.D. designed the study; J.P.D. and N.B. performed data collection; A.M.E.J. performed analysis and interpreted results with R.t.H. and R.J.M.B.; A.M.E.J., R.t.H. and R.J.M.B. drafted the manuscript; all authors critically reviewed the manuscript and approved the final version.

## Supplementary data

Figures S1–S5 are available as Supplementary data at *JAC* Online.

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