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Pharmacokinetic investigations of isavuconazole in paediatric cancer patients show reduced exposure of isavuconazole after opening capsules for administration via a nasogastric tube

Didi Bury [1,2]*, Tom F.W. Wolfs [1,3,4]†, Rob ter Heine [2]†, Eline W. Muilwijk [5], Kim C.M. van der Elst [6], Wim J.E. Tissing [1,7] and Roger J.M. Brüggemann [1,2,8]

[1]Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands; [2]Department of Pharmacy, Radboud University Medical Center, Radboud Institute for Medical Innovation, Nijmegen, The Netherlands; [3]Department of Infectious Diseases, Wilhelmina Children's Hospital/University Medical Center Utrecht, Utrecht, The Netherlands; [4]Department of Infectious Diseases, Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands; [5]Department of Pharmacy, Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands; [6]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [7]Department of Pediatric Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [8]Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands

*Corresponding author. E-mail: d.bury-3@prinsesmaximacentrum.nl
†Equally contributed to this work.

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Objectives: To study the isavuconazole pharmacokinetics in a real-life paediatric cohort and confirm whether the isavuconazole exposures are within the adult exposure range. Furthermore, we are the first to describe unbound isavuconazole pharmacokinetics.

Methods: In this prospective, observational study, the isavuconazole dosing regimen was as follows (IV/oral/nasogastric tube): 5.4 mg/kg isavuconazole (maximum 200 mg/dose) three times daily on Days 1 and 2, followed by 5.4 mg/kg isavuconazole (maximum 200 mg/dose) once daily. At least one pharmacokinetic curve was assessed. Non-linear mixed effects modelling was used for analysis. Monte Carlo simulations were performed with the above mentioned maintenance dose for IV administrations and a weight band dosing regimen for oral/nasogastric tube administrations: I) <18 kg (100 mg daily); II) 18–37 kg (150 mg daily); III) >37 kg (200 mg daily).

Results: Seventeen paediatric patients with a median age of 9 years (range 1–17) and median weight of 26.0 kg (range 8.4–78.5) were evaluated. A two-compartment model describing linear pharmacokinetics of the unbound concentrations and saturable protein binding fitted the isavuconazole concentrations best. The absolute bioavailability of isavuconazole was 41.0% (95% CI: 32.4%–50.8%). The median (IQR) simulated exposures ($AUC_{0-24h,\ SS}$) of the total isavuconazole concentrations after IV and oral/nasogastric tube administration were 87.7 mg·h/L (70.5–105.1) and 50.3 mg·h/L (39.0–62.4), respectively. The unbound isavuconazole fraction (unbound/total) ranged from 0.5% to 2.3%.

Conclusions: This study revealed low bioavailability after nasogastric tube administration with opened capsules. Isavuconazole exposures were in the expected range following IV administration. Total and unbound isavuconazole pharmacokinetics were reported with a 5-fold range in the unbound fraction.

Introduction

Paediatric patients with invasive fungal disease are treated with triazole drugs as first-line agents.[1] Posaconazole and voriconazole have shown adverse effects, and many drug–drug interactions are present.[2] Isavuconazole has shown a broad antifungal spectrum, predictable pharmacokinetics, a more favourable toxicity profile and fewer abundant drug–drug interactions compared with the other drugs in the current available phase 1 and 3 studies.[3,4] Isavuconazole has regularly been used as off-label treatment in paediatric patients but there is limited pharmacokinetic knowledge in this population.[5,6] Recently, a paediatric dosing regimen has been proposed with a loading dose of 5.4 mg/kg isavuconazole three times daily on Days 1 and 2, followed by a maintenance

dose of 5.4 mg/kg isavuconazole once daily.[7] Here, we evaluated the pharmacokinetic parameters of isavuconazole in a real-life paediatric cancer cohort. Additionally, to our knowledge we are the first to describe unbound isavuconazole pharmacokinetics.[2]

Methods

Study design and patients

This was a prospective, observational study conducted from November 2019 until December 2020 in paediatric cancer patients aged ≥1 year. Patients who received isavuconazole (IV, orally via a capsule, or enterally opened capsules via a nasogastric tube) were evaluated, after informed consent. Choices for route of administration were at the discretion of the treating physician. The procedure for administration via a nasogastric tube were as follows: the capsules were opened and the content was dissolved and added in a syringe, which was subsequently administered via the nasogastric tube. The dosing regimen was as follows: 5.4 mg/kg isavuconazole (maximum 200 mg/dose) three times daily on Days 1 and 2, followed by 5.4 mg/kg isavuconazole (maximum 200 mg/dose) once daily.[7] At least one pharmacokinetic curve was drawn at $t=0$ h, 1 h, 2–4 h, 4–6 h and 12–18 h to assess the AUC. Total and unbound isavuconazole concentrations were measured with validated bioanalytical methods (see Supplementary Material, available as Supplementary data at *JAC* Online).

Ethics

All patients signed a general informed consent for participation in scientific research in the Princess Máxima Center, Utrecht, The Netherlands. For the isavuconazole study, we received approval from the Medical Ethics Committee of Utrecht (21–342/C).

Pharmacokinetic analysis

The pharmacokinetic analysis of isavuconazole was performed using non-linear mixed effects modelling (NONMEM), with the software package NONMEM V7.5 (Icon, Dublin, Ireland). Total and unbound isavuconazole concentrations were described integrally using a saturable protein binding model. Model development was based on physiological plausibility, statistical significance, and goodness-of-fit in line with best practice. The details of the analysis and model evaluation are described in Supplementary Material, Table S1 and Figures S1–S5.

The final pharmacokinetic model was used to evaluate the isavuconazole exposure after oral and IV dosing regimens by means of Monte Carlo simulations. Total isavuconazole concentrations were the main outcome parameter. For IV administrations, simulations were performed with the maintenance dose of 5.4 mg/kg/dose except for those children with a bodyweight ≥37 kg, who received a fixed dose of 200 mg. For oral and nasogastric tube administrations, a weight band dosing regimen was evaluated. The three oral dosing regimens were chosen as follows: I: <18 kg—maintenance dose of 100 mg once daily; II: 18–37 kg—alternating maintenance dose of 100–200 mg once daily (simulated as 150 mg once daily); and III: >37 kg—maintenance dose of 200 mg once daily.

For the simulations we used a dataset with demographic data (and their distribution) of a paediatric haematology cohort ($n=590$) of the Dutch Childhood Oncology Group. We compared the paediatric exposure range with the exposure range in adults [AUC at steady state (AUC_{ss})] of 60–233 mg·h/L.[7–9]

Results

A total of 17 paediatric patients with a median age of 9 years (range 1–17 years) and median weight of 26.0 kg (range 8.4–78.5 kg) were evaluable. The isavuconazole treatment duration ranged from 11 to 546 days. An overview of the indication specifics is given in Table S2.

A total of 119 total and 43 unbound isavuconazole concentrations were available for analysis on 26 sampling occasions. The route of administration at these sampling occasions was IV ($n=17$), oral via a capsule ($n=1$) and enteral via a nasogastric tube ($n=8$).

The measured unbound isavuconazole concentrations ranged from 0.01 to 0.2 mg/L, and the total isavuconazole concentrations ranged from 1.08 to 11.6 mg/L. The unbound isavuconazole fraction varied almost 5-fold, ranging from 0.5% to 2.3% (Figure S2), and the unbound fraction increased with increasing unbound concentrations.

Population pharmacokinetic analysis

A two-compartment linear pharmacokinetic model with a saturable protein model binding described the isavuconazole concentrations best (Figure S1).

The absolute bioavailability (F) of isavuconazole was estimated to be 41.0% (95% CI: 32.4%–50.8%). The unbound CL (CL_u) was 337 L/h (95% CI: 281–413 L/h). One patient received interacting co-medication (phenobarbital), which was found to increase CL_u by 2.42 (95% CI: 1.36–4.12) times.

The median (IQR) simulated $AUC_{0-24h,\ SS}$ of the total isavuconazole concentrations after IV and oral/nasogastric tube administration were 87.7 mg·h/L (95% CI: 70.5–105.1) and 50.3 mg·h/L (95% CI: 39.0–62.4), respectively. The predicted isavuconazole exposures after IV and enteral routes of administration are depicted in Figure 1. The adult exposure range ($AUC_{0-24h,\ SS}$ 60–233 mg h/L) was reached in 90% of the simulated patients after IV administration and in 29% of the simulated patients after enteral administration.

Discussion

Our most important finding is the observed low isavuconazole exposure following enteral administration of the recommended

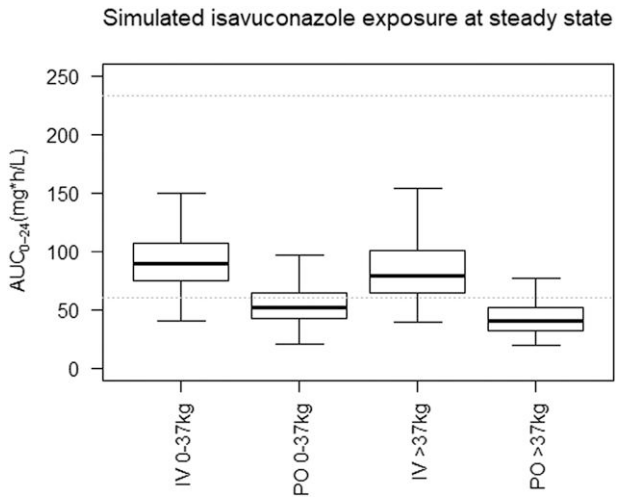

Figure 1. Predicted isavuconazole exposure after IV and oral (PO) administration. The dashed lines indicate the lower (AUC_{ss} of 60 mg·h/L) and upper (AUC_{ss} of 233 mg·h/L) bound of the exposure in adult patients.

isavuconazole regimen in our paediatric cohort when compared with a recent phase I paediatric study.[7]

We found an absolute isavuconazole bioavailability of 41.0%, which contradicts the bioavailability of 95% and 98% reported in immunocompromised paediatric patients and healthy adults, respectively.[2,7] To explain this difference, we attempted to identify sources of variability within our population. The majority of our patients on enteral therapy received isavuconazole capsules over the nasogastric tube. Previously, adequate exposure has been reported after giving the IV solution over the nasogastric tube in healthy adult participants.[10] At the start of our study this information was not known. Therefore, the capsules were opened and the dissolved content was administered via a tube. The handling of the capsules may have caused a loss of content. Furthermore, the drug is, according to the Stabilis database (https://www.stabilis.org/), stable for 1 h at room temperature. The hygroscopic nature of isavuconazium sulphate causes instability of the prodrug and may have caused additional loss of content. However, in literature, comparable trough concentrations were reported after IV administration versus oral tube administration with opened capsules in 19 adult patients.[11] The potential impact of lower oral bioavailability might have been blurred in that study where 13 out of 19 patients received isavuconazole IV prior to the switch to oral treatment over a tube. Given the long terminal half-life of isavuconazole, it might take several days to weeks before the low exposure after tube administration becomes apparent.

We hypothesize that the administration of opened capsules and subsequently dissolved content over the nasogastric tube might be responsible for the low exposure after oral administration in our study. As our study was not designed to elucidate the root cause for low bioavailability, other factors like age-dependent oral absorption, may not be ruled out. This has previously been seen in a cohort of paediatric patients receiving voriconazole: the authors hypothesized that changes in intestinal first-pass metabolism might explain the difference in bioavailability between paediatric patients and adults irrespective of oral formulation.[12] Currently, reports do not point towards such a mechanism resulting in reduced oral bioavailability in a cohort of paediatric patients.[7]

We acknowledge that our study consisted of a relatively small sample size. The obtained real-world pharmacokinetic data consequently led to the inclusion of a wide range of age, weight and treatment duration. Therefore, our findings should be carefully interpreted. Furthermore, our sampling strategy, contrary to the phase I paediatric report, lacks intensive sampling during the absorption phase.[7] Although a more intensive sampling strategy would have given more information on the absorption rate, it would not likely have altered our findings on the bioavailability of isavuconazole. Lastly, just one patient received isavuconazole orally versus eight patients receiving isavuconazole over the nasogastric tube. As a result, a comparison with orally administered capsules could not be made. The impact of administration of opened capsules and subsequently dissolved content over the nasogastric tube should be confirmed in a larger cohort of patients. Until then, we recommend using the reconstituted injection formulation for nasogastric tube administration, combined with therapeutic drug monitoring.[10] The IV fluid contains sulphuric acid and is stable for 6 h at room temperature. Stability issues as observed for the oral formulation may thus be less pronounced.

The main goal of our study was to investigate pharmacokinetics of isavuconazole in paediatric cancer patients. We predicted that in 90% of the paediatric patients the (total) isavuconazole exposure reached the exposure in adults on a population level after IV administration. Although these findings cannot be directly compared with the phase I paediatric study, this predicted exposure is of the same order of magnitude as reported by the manufacturer (>80%).[7]

We also reported on total and unbound isavuconazole concentrations. Our analysis of unbound (active) isavuconazole concentrations reveals a 5-fold total range in the unbound isavuconazole fraction (Figure S2), which is much larger than the reported range in the EMA assessment report.[2] When the fraction of unbound concentration varies widely, total concentrations may not correctly reflect the pharmacologically active fraction of isavuconazole. Hence, we recommend future research to focus on unbound isavuconazole concentrations.

In conclusion, isavuconazole enteral bioavailability was reduced in paediatric cancer patients. Clinicians should be aware of lower isavuconazole exposures after administration over a nasogastric tube. Administration of the reconstituted injection formulation over the nasogastric tube could be considered in combination with therapeutic drug monitoring. Furthermore, we propose utilizing unbound drug concentrations for therapeutic drug monitoring and defining target concentrations associated with efficacy and toxicity.

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Transparency declarations

No conflicts of interest/competing interests are applicable for this work. Disclosures outside of this work: R.J.M.B. has served as a consultant to Astellas Pharma, Inc., F2G, Amplyx, Gilead Sciences, Merck Sharp & Dohme Corp., Mundipharma and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharp & Dohme Corp. and Pfizer, Inc. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. None of the other authors have a conflict to declare.

Author contributions

Design of the protocol: D.B., T.F.W.W., W.J.E.T. and R.J.M.B. Data collection: D.B. Interpretation of the data: D.B., W.J.E.T., R.H., W.J.E.T. and R.J.M.B. Formal statistical analysis: D.B., R.H. and R.J.M.B. Writing original draft: D.B., T.F.W.W., R.H., W.J.E.T. and R.J.M.B. Critical revision draft: E.W.M. and K.C.M.E. Editing draft: D.B., T.F.W.W., R.H., W.J.E.T. and R.J.M.B. All authors provided approval of the final version.

Supplementary data

Figures S1–S5, Tables S1 and S2, and Supplementary Material are available as Supplementary data at *JAC* Online.

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