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# Pharmacokinetics and target attainment of intravenous posaconazole in critically ill patients during extracorporeal membrane oxygenation

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**Background:** Posaconazole is an antifungal drug used for prophylaxis and treatment of invasive fungal infections. Severe influenza has been identified as a risk factor for invasive pulmonary aspergillosis in critically ill patients. In this population, extracorporeal membrane oxygenation (ECMO) is used as rescue therapy, although little is known about the pharmacokinetics (PK) of posaconazole during ECMO.

**Objectives:** To determine the PK and target attainment of six patients treated with IV posaconazole under ECMO and to develop a population PK model that can be used to simulate the PTA.

**Methods:** Critically ill patients treated with posaconazole and ECMO were included in this study. Plasma samples were collected at several timepoints within one dosing interval on two occasions: an early (Day 2–3) and a late (Day 4–7) sampling day. Daily trough concentrations were measured.

**Results:** The median (IQR) $AUC_{0-24}$, CL and $V_d$ were 34.3 (28.3–37.7) mg·h/L, 8.7 (8.0–10.6) L/h and 389 (314–740) L, if calculated with non-compartmental analysis based on the observed concentrations. All measured trough concentrations were ≥0.7 mg/L and 11/16 were ≥1 mg/L, which are the haematological thresholds for prophylaxis and treatment of invasive aspergillosis, respectively. The targeted PTA (>90%) was attained for prophylaxis but not for treatment.

**Conclusions:** ECMO does not appear to influence posaconazole exposure compared with haematology patients. However, some trough levels were below the lower limit for treatment. An *a priori* dose adjustment does not appear to be necessary but drug monitoring is recommended.

## Introduction

Posaconazole is a broad-spectrum triazole antifungal drug registered for prophylaxis of invasive fungal infections in neutropenic patients treated with chemotherapy for AML or myelodysplastic syndromes. It is also approved for prophylaxis in patients suffering from severe graft-versus-host disease after HSCT. In both indications, posaconazole has significantly decreased the incidence of invasive aspergillosis.[1,2] Posaconazole is also used as salvage therapy for invasive aspergillosis and other mycoses.[3]

When used as prophylaxis in the haematological setting, therapeutic drug monitoring (TDM) for posaconazole is recommended in the European Conference on Infections in Leukaemia (ECIL6) guidelines with target trough concentrations ($C_{min}$) above 0.7 mg/L associated with a lower risk for breakthrough infections.[4] When used in treatment, TDM is also advised and a $C_{min}$ target of 1 mg/L is recommended for invasive aspergillosis.[4,5] At this moment, there are insufficient data to recommend an upper limit for safety[4] but during the drug development of the tablet and IV formulations the EMA used a concentration of 3.75 mg/L as the maximum

average steady-state plasma concentration with a target range between 0.5 and 2.5 mg/L.[6,7] Besides target (trough) levels, therapeutic success can also be defined as a total $AUC_{0-24}$/MIC of 167–178,[8,9] leading to a target $AUC_{0-24}$ of 20.9–22.5 mg·h/L for an MIC value of 0.125 mg/L, which is the EUCAST clinical breakpoint for susceptibility for non-resistant *Aspergillus fumigatus* and *Aspergillus terreus*.[9,10]

Severe influenza was recently identified as an independent risk factor for the development of invasive pulmonary aspergillosis in critically ill patients.[11–13] Influenza-associated pulmonary aspergillosis (IAPA) is associated with a high mortality of up to 51%,[12] so posaconazole is explored as antifungal prophylaxis in this population (ClinicalTrials.gov NCT03378479). For patients with refractory hypoxaemia despite maximum conventional ventilator support, extracorporeal membrane oxygenation (ECMO) can be used as a rescue therapy to replace the function of the failing lungs. A major challenge in patients treated with ECMO is obtaining adequate drug exposure as pharmacokinetics (PK) might be altered due to a larger volume of distribution ($V_d$), caused by priming of the circuit and/or adsorption of the drug to the surface of the ECMO circuit.[14] It has previously been shown that the PK of voriconazole are altered in patients on ECMO, necessitating substantially higher dosing based on frequent TDM.[15–17] To date, there are no data available on the impact of ECMO on the exposure and target attainment of posaconazole. Target attainment of posaconazole can already be challenging due to high inter- and intra-individual PK variability, which although improved are still present with the new posaconazole formulations.[18] Moreover, one might expect that posaconazole would at least be partially lost due to sequestration in the ECMO circuit, since it is a highly lipophilic molecule that is characterized by an octanol/water partition coefficient (logP value) of 5.5 and by high protein binding (>98%).[18–20] Moreover, an influence of critical illness might be expected. Generally, this could be observed by an increased $V_d$, altered hepatic metabolism or renal elimination, and hypoalbuminaemia.[21] However, posaconazole is predominantly excreted via bile as an unchanged molecule; it shows only limited hepatic metabolism and only negligible amounts are excreted unchanged in urine. Not much influence of metabolism, excretion and renal replacement therapy is expected.[22,23] Hypoalbuminaemia, in contrast, could influence posaconazole concentrations as it is highly protein-bound. The free fraction of posaconazole might increase and consequently result in higher distribution and excretion.[22–24] There is an urgent need for more information to ensure adequate exposure to posaconazole in ECMO-treated critically ill patients.

The goal of this study was to evaluate the PK and target attainment of IV posaconazole in critically ill patients undergoing ECMO. First, the PK parameters and target attainment were calculated based on the observed posaconazole concentrations. Second, to support the observed data, a population pharmacokinetic (PopPK) model was developed and used to simulate the PTA.

## Materials and methods

### Study design and population

All adult, critically ill patients treated simultaneously with IV posaconazole and ECMO between January 2018 and April 2019 were included, provided they did not have a Do Not Resuscitate (DNR) code higher than 1 and written informed consent was obtained from the patient or his/her relatives. Since this was an explorative study, no formal sample size calculation was performed. Five of the included patients were participating in a prospective multicentre study (Posa-Flu study, ClinicalTrials.gov NCT03378479). In brief, patients admitted to the ICU due to severe influenza were randomized to either IV posaconazole prophylaxis for 7 days or a standard-of-care diagnostic workup in 12 hospitals in Belgium, the Netherlands and France. The patients included in this report were hospitalized in one of two Belgian hospitals: the University Hospitals Leuven (UZ Leuven) or Ghent University Hospital (UZ Ghent). In all patients, posaconazole was given IV as a loading dose of 300 mg q12h on Day 1, followed by a maintenance dose of 300 mg q24h starting on Day 2, with an infusion duration of 90 min. This study was conducted in accordance with the Declaration of Helsinki and good clinical practice regulation. The Posa-Flu study was approved by the Ethics Committees in Belgium, the Netherlands and France (S60744, NL64151.091.18 and 18 89).

### Extracorporeal circuits

Each study site used its own ECMO circuits. In UZ Leuven, the ECMO circuits consisted of rheoparin-coated tubing (Medos Tubing Sets®, Heilbronn, Germany), a DP3 pump generating the flow rate (Medos Deltasteam®, Heilbronn, Germany), a 1.9 $m^2$ polymethylpentene membrane oxygenator (Medos HILITE® 7000 LT) and a polyester heat exchanger. In UZ Ghent, a PLS tubing set (Getinge®, Sweden) was used. This is a pre-connected standard set consisting of a PLS-i oxygenator (polymethylpentene 1.8 $m^2$) and a Rotaflow centrifugal pump RF-32, both incorporated into a tubing set with tip-to-tip bioline (albumin–heparin) coating. All ECMO circuits were primed with Plasmalyte®.

Two patients were concomitantly treated with continuous veno-venous haemodialysis (CVVH) during the administration of posaconazole.

### Sample collection

Blood samples were collected over a full dosing interval (24 h) on both an early day (i.e. Day 2 or 3, after at least the full loading dose was administered) and a later day (i.e. Day 4–7) of posaconazole administration. Two sampling schemes were available for this 24 h collection, depending on practical and logistic capacities of the study sites. In sites with extended PK sampling capacity, plasma samples were taken pre-dose, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24 h post-infusion ($n = 11$), while sites with limited PK sampling collected samples pre-dose, 1.5–3, 4–8, 8–12, 12–24 and 24 h post-infusion ($n = 6$). On all other days until Day 7, trough samples were taken. Blood samples were collected in lithium heparin-containing tubes and immediately stored at 4–8°C. Within 7 days, the samples were centrifuged for ∼10 min at 1910 **g** and stored at −80°C until analysis.

### Method of analysis

Posaconazole concentrations were determined by an HPLC system with UV detection at 260 nm (1200 Agilent Technologies, Diegem, Belgium) in the clinical chemistry laboratory of the LHUB-ULB. The separation was performed on an XBridge Phenyl (Waters, Zellik, Belgium) column (4.6 × 150 mm, 3.5 μm diameter particles). In brief, 500 μL of plasma, 100 μL of internal standard (bifonazole 5 mg/L) and 125 μL of 16% ammonium hydroxide were added together. Three millilitres of hexane/dichloromethane 1:1 (v/v) was used for the extraction, after which the organic layer was dried under nitrogen, then 150 μL of methanol and 150 μL of 20 mM bicarbonate ammonium (pH 10.0) were used to dissolve the extract and 50 μL was subsequently injected into an HPLC-UV instrument. The mobile phase consisted of the same bicarbonate ammonium buffer (pH 10.0) mixed with acetonitrile/bicarbonate buffer (80/20) in a gradient ranging from 55:45 to 100:0 (v/v). The lower limit of quantification of the method was 0.2 mg/L with a linearity range between 0.3 and 10 mg/L. The method was validated according to the International Council for Harmonisation of

Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and externally validated by an international proficiency testing programme (SKML EQA programme).[25,26]

### Non-compartmental PK analysis

PK parameters were first determined by non-compartmental analysis (NCA) using Excel®. The $AUC_{0-24}$ was determined using the log-linear trapezoidal rule. The elimination rate constant (k) was determined as the slope of the terminal part of the ln(concentration)–time curve. Half-life was determined as ln2/k. Plasma CL was calculated as dose/$AUC_{0-24}$ and $V_d$ as dose/k·$AUC_{0-24}$. Average concentrations ($C_{avg}$) were determined as $AUC_{0-24}$/24 h. In the case of the last trough level of a 24 h collection missing, this level was estimated by linear regression and extrapolation on the terminal part of the ln(concentration)–time curve.

### PopPK modelling

PopPK modelling was performed with non-linear mixed-effects modelling using the software NONMEM version 7.4, with Pirana as an interface for the GNU Fortran 95 compiler and Perl-speaks-NONMEM. Exploratory graphical and statistical data analyses were performed in R, version 3.5.1. Based on visual inspection of the data and a literature review, one- and two-compartment PopPK models with linear elimination were developed and the most parsimonious model was withheld.[24,27–34] No covariates were included due to the limited dataset. With the final PK model, a stochastic PK simulation was performed for 1000 patients over 7 days under the standard dosage regimen (300 mg q24h, after a loading dose of 300 mg q12h on Day 1). Trough concentration targets of 0.7 mg/L (prophylaxis) and 1.0 mg/L (treatment) were chosen to determine the PTA. A PTA of ≥90% was considered adequate. More information about PopPK modelling and simulation is presented in the Supplementary data, available at *JAC* Online.

## Results

### Study population

During a 15 month study period, six patients concomitantly treated with posaconazole and ECMO were included. Five of them were given posaconazole as prophylaxis for IAPA in the context of the Posa-Flu trial. One additional patient was included after receiving posaconazole prophylaxis pre-and post-lung transplantation, after informed consent was provided. All patients received veno-venous ECMO and all ECMO treatments started only 1 day before or on the same day as the initiation of posaconazole treatment.

Ideally, patients were followed for 7 days but in some cases posaconazole was discontinued before the later sampling day or sometimes ECMO was only associated for one of the two sampling days. Three patients completed both the early and later sampling day while on ECMO, two patients were only sampled on an early day (Day 2) and one patient was only sampled on Day 6. For four patients, the extended sampling procedure was followed; the remaining two patients completed the limited sampling scheme. In two cases, the last trough level of the 24 h collection was estimated due to missing data.

Patients had a median (IQR) age of 44 (40–57) years and BMI of 31.6 (27.9–33.5) kg/m$^2$. The median (IQR) length of ICU stay was 22 (18–27) days and two out of six patients died during their ICU stay. The median (IQR) APACHE II score was 19.0 (18.3–19.8). A total of 83 posaconazole samples were collected: 81 levels as part of a 24 h PK profile and two additional trough levels. Baseline patient characteristics of the included patients are shown in Table 1.

**Table 1.** Patient characteristics

| Characteristic ($n = 6$) | |
|---|---|
| Demographics | |
| Age (years), median (IQR) | 44 (40–57) |
| Sex, male, *n* (%) | 3 (50) |
| Weight (kg), median (IQR) | 76 (67–97) |
| BMI (kg/m$^2$), median (IQR) | 31.6 (27.9–33.5) |
| Medical history | |
| COPD, *n* (%) | 1 (17) |
| Diabetes, *n* (%) | 2 (33) |
| Organ transplantation, *n* (%) | 1 (17) |
| Chronic kidney insufficiency, *n* (%) | 1 (17) |
| Clinical characteristics | |
| Length of ICU stay (days), median (IQR) | 22 (18–27) |
| Died during ICU stay, *n* (%) | 2 (33) |
| APACHE II score on ICU admission, median (IQR) | 19.0 (18.3–19.8) |
| SOFA score on sampling day, median (IQR) ($n = 9$) | 11 (8–12) |
| Extracorporeal circuits | |
| Veno-venous ECMO, *n* (%) | 6 (100) |
| CVVH, *n* (%) | 2 (33) |

### Non-compartmental PK analysis

The median (IQR) $AUC_{0-24}$, CL and $V_d$ were 34.32 (28.25–37.68) mg·h/L, 8.7 (8.0–10.6) L/h and 389 (314–740) L. The median $C_{min}$ was 1.11 (0.98–1.32) mg/L and the median (IQR) $C_{avg}$ was 1.43 (1.18–1.57) mg/L. Table 2 summarizes the median (IQR) PK parameters for posaconazole during ECMO. In order to allow comparison, previously reported results, documented in healthy volunteers, patients with haematological disease and critically ill patients, were also included in Table 2. Figure S1 shows posaconazole trough concentrations of all included patients.

### PopPK modelling

A two-compartment PK model with first-order elimination best described the data (Figure S2). Parameter estimates of the structural, inter-individual variability and residual error models are included in Table 2. Using the typical parameter values, the volume of distribution of the peripheral compartment at steady state ($V_p$) was estimated as 396 (11%) L, the distribution half-life $t_{1/2,\alpha}$ as 0.13 (1%) h and the elimination half-life $t_{1/2,\beta}$ as 40.5 (22%) h. More detailed information on the PopPK modelling can be found in the Supplementary data, including goodness-of-fit plots (Figure S3), visual predictive check (Figure S4) and individual concentration–time profiles (Figure S5).

### Target attainment

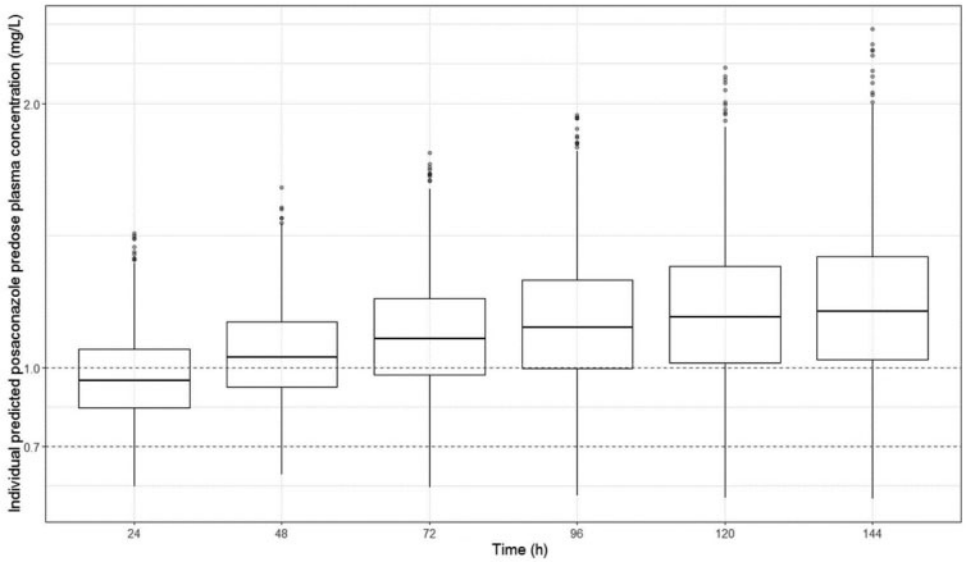
All observed trough levels were ≥0.7 mg/L and 11 out of the 16 (68.8%) observed $C_{min}$ values were ≥1 mg/L (Figure S1). The estimated trough levels, based on the PTA analysis, supported these observed results since an adequate target attainment (>90%) in ECMO patients was shown in prophylaxis throughout 7 days of posaconazole administration (Figure 1). However, the probability of attaining the lower level for treatment (1 mg/L) was below 90%

**Table 2.** PK parameters of posaconazole documented in patients undergoing ECMO versus previously reported results from literature

| Study population | This study | | Kersemaekers *et al.*[36] mean (%CV) | Cornely *et al.*[35] mean (%CV) | Sime *et al.*[23] median (IQR) |
|---|---|---|---|---|---|
| *n* | 6 | | 9 | 49 | 8 |
| | Calculated PK parameter based on measured 24 h posaconazole plasma profiles, median (IQR) | Estimated values based on two-compartment PK model, RSE [η-shrinkage] | Healtdy volunteers Single dose (300 mg) peripheral administered posaconazole | Haematological patients Standard (loading dose + 300 mg q24h) IV posaconazole dosing for at least 9 additional days | Critically ill patients (no ECMO) Single dose (300 mg) IV posaconazole |
| PK parameters | | | | | |
| $AUC_{0-24}$ (mg·h/L) | 34.32 (28.25–37.68) | | 46.40 (26) ($AUC_{0-\infty}$) | 36.1 (35) | 11.61 (9.9–18.25) ($AUC_{0-24}$) |
| corrected for body weight | 0.40 (0.35–0.71) mg·h/L/kg | | | | 17.93 (13.82–27.91) ($AUC_{0-\infty}$) |
| CL (L/h) | 8.7 (8–10.6) | 7.7 [11%] | 6.9 (27) | | 16.8 (11.1–21.7) |
| corrected for body weight | 0.12 (0.1–0.16) L/h/kg | | | | |
| Q (L/h) | | 128 [22%] | | | |
| $V_d$ (L) | 389 (314–740) | | 236 (17) (terminal phase) | | 529.1 (352.2–720.6) |
| corrected for body weight | 6.15 (3.96–9.25) L/kg | | | | |
| $V_c$ (L) | | 26.2 [60%] | | | |
| $V_p$ (L) | | 396 [11%] | | | |
| $t_{1/2}$ (h) | 33.6 (27.3–53) | | 24.6 (20) | | 23 (19.1–31.6) |
| $t_{1/2,\alpha}$ (h) | | 0.13 [1.3%] | | | |
| $t_{1/2,\beta}$ (h) | | 40.5 [22.4%] | | | |
| $C_{min}$ (mg/L)[a] | 1.11 (0.98–1.32) | | | 1.09 (44) | 0.22 (0.2–0.56) |
| $C_{max}$ (mg/L) | 2.47 (1.91–3.38) | | 2.84 (30) | 3.28 (74) | 1.70 (1.35–2.14) |
| $C_{avg}$ (mg/L) | 1.43 (1.18–1.57) | | | 1.5 (35) | 0.75 (0.58–1.16) (estimated) |
| Variability (%CV) | | | | | |
| CL | | 21.8 (21) [6%] | | | |
| $V_p$ | | 23.4 (28) [7%] | | | |
| Proportional residual error | | 1.79 (9) [5%] | | | |

Q, intercompartmental clearance; $V_c$, volume of distribution in the central compartment; %RSE, relative standard error, expressed as a percentage; %CV, coefficient of variation, expressed as a percentage, calculated as $\%CV = \sqrt{\exp(\omega^2) - 1} \times 100\%$.

[a]Value calculated based on all measured trough concentrations and not only the trough levels included in the 24 h PK profile.




| | | | | | | |
|---|---|---|---|---|---|---|
| Concentration (mg/L) | 1.0 ±0.2 | 1.1 ±0.2 | 1.1 ±0.2 | 1.2 ±0.2 | 1.2 ±0.3 | 1.2 ±0.3 |
| PTA [0.7 mg/L] (%) | 95 | 98 | 98 | 98 | 98 | 98 |
| PTA [1.0 mg/L] (%) | 39 | 59 | 70 | 75 | 77 | 79 |

**Figure 1.** Individual-predicted posaconazole pre-dose plasma concentrations over time of 1000 simulated patients. The boxes represent the medians (solid lines) and IQRs. Horizontal broken lines indicate the thresholds for prophylaxis (0.7 mg/L) and treatment (1 mg/L).

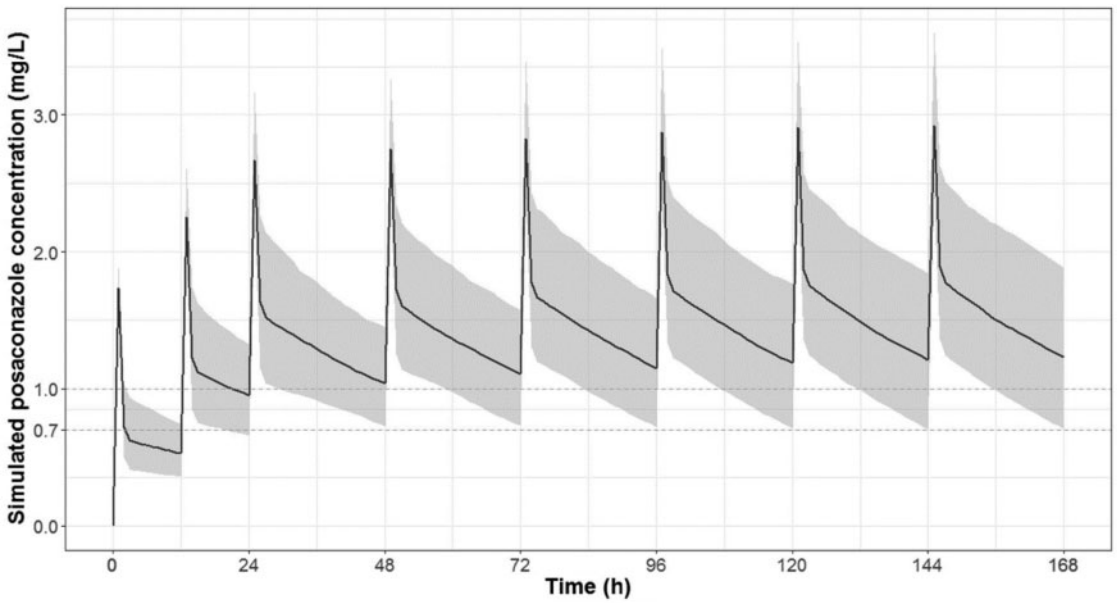



**Figure 2.** Simulated posaconazole plasma concentration–time profile following standard dosing. Data represent the median and the 95% prediction interval of 1000 simulated patients.

(39%–79%, depending on the day of administration) (Figures 1 and 2). Moreover, the $C_{avg}$ of the observed data fell within the EMA target range (0.5–2.5 mg/L).[6] Besides the target concentrations, the pharmacodynamic (PD) target was also of interest. This target was attained since the calculated $AUC_{0-24}$ was above 22.5 mg·h/L, assuming an MIC value equal to the EUCAST clinical breakpoint for susceptibility of 0.125 mg/L for *Aspergillus* spp.[9,10]

## Discussion

In this study, posaconazole PK and target attainment were documented for the first time, to the best of our knowledge, in critically ill patients receiving ECMO. ECMO did not appear to substantially modify PK parameters of IV posaconazole, compared with non-ICU haematology patients. Target trough concentrations for prophylaxis were attained; however, not all patients attained a trough concentration ≥1 mg/L for treatment. The impact of the pathophysiological changes associated with critical illness as such is still to be clarified.

As shown in Table 2, the exposure in this study population ($AUC_{0-24}$ 34.32 mg·h/L) was similar to that found in haematology patients ($AUC_{0-24}$ 36.10 mg·h/L)[35] and a little lower than that documented in healthy volunteers ($AUC_{0-\infty}$ 46.40 mg·h/L).[36] Interestingly, a recent study showed a 3-fold lower $AUC_{0-24}$ (11.6 mg·h/L) in ICU patients without ECMO.[23] Consequently, a difference in $V_d$ (389 versus 529 L) and CL (8.7 versus 16.8 L/h) was observed. This is remarkable because the patients in our study were also critically ill and, in addition, they were treated with ECMO, which might hypothetically further decrease the exposure and increase the $V_d$. However, Sime *et al.*[23] calculated the PK parameters after one single dose of 300 mg posaconazole whereas patients in this study received at least a full loading dose (300 mg q12h) before sample collection. A gradual increase in exposure after multiple administrations can be observed in this study, which could explain the higher exposure (Figure 2 and Figure S1). However, it cannot be excluded that this increasing exposure is due to saturation of the ECMO circuit since ECMO was initiated on the same day or 1 day before initiation of posaconazole treatment.

Target attainment for posaconazole was evaluated. The target $AUC_{0-24}$ was attained and the $C_{avg}$ fell within the EMA target range. Despite the fact that the lower limits for prophylaxis in critically ill patients are not yet known, it is reassuring to see that the threshold proposed for prophylaxis used in patients with haematological disease was reached for all posaconazole trough concentrations. Nevertheless, the lower limit recommended for treatment of invasive aspergillosis was not always attained. This was confirmed in the PK simulations, in which the predicted PTA for prophylaxis was >90% but the probability of attaining the lower level for treatment (1 mg/L) was below 90% (39%–79%, depending on the day of administration) (Figure 1). It might be debatable whether these subtherapeutic concentrations for treatment are attributable to critical illness and ECMO since levels below 1.25 mg/L have also been shown in non-critically ill patients (34%), even with the standard dosing of the novel tablet formulation.[37]

No upper limit for toxicity was taken into account for the simulations since no (evidence-based) relationship between exposure and toxicity has been observed for posaconazole.[18] Moreover, as shown in Figure 2, simulated trough levels did not exceed the 3.75 mg/L threshold used by the EMA.[6]

It seems that the impact of ECMO is not as significant as might be expected. Posaconazole exposure in our cohort was not very different from that measured in haematology patients. This was also confirmed in a patient in whom the posaconazole concentration was similar before and after the ECMO membrane (1.2 and 1.3 mg/L) (non-published data). Based on the lipophilicity and high protein binding of posaconazole, one might have expected a lower posaconazole exposure, since especially highly lipophilic and highly protein-bound drugs are prone to sequestration to the ECMO circuit.[19] Later on, it might be expected that binding sites are saturated, potentially leading to drug accumulation in plasma. This has already been described before for voriconazole, which is also lipophilic (logP of 1).[38] In an *ex vivo* ECMO simulation model, voriconazole concentrations were decreased by 56% by the end of a 24 h period.[15] Afterwards, clinical case reports confirmed this decrease in voriconazole concentrations.[16,17] Besides voriconazole, sequestration to the ECMO circuit has been documented for other commonly used ICU drugs (e.g. midazolam, lorazepam, propofol and fentanyl).[39,40] To determine the effect of sequestration for posaconazole and the possible influence on its exposure, *ex vivo* experiments should be performed. In our opinion, the limited impact of ECMO and/or critical illness might be explained by the large $V_d$ of posaconazole; hence critical illness and ECMO might lead to only minimal relative increases in $V_d$ compared with the total $V_d$. Moreover, as mentioned above, the influence on hepatic metabolism and renal excretion is expected to be low due to the predominant excretion via bile, although hypoalbuminaemia might influence the total posaconazole concentrations. The importance of albumin concentrations, and also BMI, has been shown in critically ill patients using a PopPK model for both total and unbound posaconazole concentrations.[24] More research is needed to further elucidate posaconazole exposure in critically ill patients.

An important limitation of this study is the relatively small dataset. Ideally, more patients should be sampled to draw more definite conclusions. However, for patients on ECMO, a sample size of six patients is very reasonable. Moreover, similar sample sizes are used in drug-developing substudies determining the influence of liver and kidney failure. To the best of our knowledge, this is the first report about this topic so, although limited, this dataset provides valuable results.

Based on our results, an *a priori* dose adjustment does not seem to be necessary in clinical practice but we think it is prudent to use TDM to warrant both early and late exposure in both prophylaxis and, certainly, in treatment. Ideally, a patient-specific target in critically ill patients should be determined and used, so a target trough level should be determined in this population.

### *Conclusions*

ECMO does not appear to influence posaconazole exposure compared with haematology patients and haematological prophylaxis targets were attained. The majority of, but not all, trough levels were also above the lower limit for treatment. No *a priori* dosing modification appears to be needed. However, TDM is recommended to guarantee exposure, especially if higher targets are aimed for. To the best of our knowledge, this is the first study reporting on posaconazole exposure during ECMO but more research is needed.

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## Transparency declarations

R.V.D. reports non-financial support from Pfizer Inc. and non-financial support from Gilead Sciences, outside the submitted work. R.J.B. reports being a consultant to F2G and Amplyx and has received unrestricted grants in the past 5 years from Gilead, Pfizer, MSD and Astellas. He has provided lectures for Gilead and Pfizer. All contracts were with Radboudumc and all invoices were paid to Radboudumc. E.D. is a postdoctoral research fellow of the Research Foundation—Flanders (FWO), Belgium (grant number 12X9420N) and has received consultancy fees from argenx and Janssen (all honoraria/fees paid to the university). M.G. reports personal fees from Pfizer Inc., outside the submitted work. J.W. reports grants from MSD during the conduct of the study, grants and other support from MSD, other support from Gilead and grants and other support from Pfizer, outside the submitted work; and MSD provided posaconazole vials and an investigator-initiated grant for this study. I.S. reports travel grants and speaker fees from Merck and Pfizer. P.D., B.R., F.C., D.F., K.v.Z. and Y.D. have nothing to disclose.

## Supplementary data

Figures S1 to S5 and Supplementary methods, results and references are available as Supplementary data at *JAC* Online.

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