PHARMACOKINETICS OF INTRAVENOUS POSACONAZOLE

IN CRITICALLY ILL PATIENTS

Fekade B Sime, Janine Stuart, Jenie Butler, Therese Starr, Steven C Wallis, Saurabh Pandey, Jeffrey Lipman, Jason A Roberts

School of Pharmacy, Centre for Translational Anti-infective Pharmacodynamics, The University of Queensland, Brisbane Australia; Department of Intensive Care Medicine, Royal Brisbane and Women’s Hospital, Brisbane Australia; University of Queensland Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane Australia; Pharmacy Department, Royal Brisbane and Women’s Hospital, Brisbane Australia

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# Address correspondence to Jason A Roberts, j.roberts2@uq.edu.au

Faculty of Medicine, UQ Centre for Clinical Research, Building 71/918, Herston Rd, Herston, Queensland, Australia 4029

Ph +61 7 3346 5032 Fax +61 7 3646 3542
Abstract

To date, there is no information on the IV posaconazole pharmacokinetics in ICU patients. This prospective observational study aimed to describe the pharmacokinetics of a single dose of IV posaconazole in critically ill patients. Patients with no history of allergy to triazole antifungals and requiring systemic antifungal therapy were enrolled if aged ≥ 18 years, central venous access was available, were not pregnant, and didn’t receive prior posaconazole or drugs interacting with posaconazole. A single dose of 300 mg posaconazole was administered over 90 minutes. Total plasma concentrations were measured from serial plasma samples collected over 48 h, using a validated chromatographic method. The pharmacokinetic data set was analyzed by non-compartmental methods. Eight patients (7 male) were enrolled; median (interquartile range, IQR) age 46 years (40-51), weight 68 kg (65-82) and albumin concentration 20 g/L (18-24). Median (IQR) pharmacokinetic parameter estimates were Cmax, 1,702 ng/mL (1,352-2,141); AUC0-∞, 17,932 ng*h/mL (13,823 – 27,905); CL, 16.8 L/h (11.1-21.7); and Vd, 529.1 L (352.2 – 720.6).

The Vd and CL were greater than two fold and AUC0-∞ was 39% of values reported for healthy volunteers. The AUC0-∞ was only 52% of the steady-state AUC0-24 reported for hematology patients. The median of estimated average steady-state concentrations was 747 ng/mL (IQR, 576 -1,163), which is within but close to the lower end of previously recommended therapeutic range of 500 to 2,500 ng/mL. In conclusion, we observed different pharmacokinetics of intravenous posaconazole in this cohort of critically ill patients compared to healthy volunteers and hematology patients.
INTRODUCTION

Treatment of fungal infections remains a significant challenge to clinicians, particularly for critically ill patients requiring intensive care unit (ICU) management where the incidence of invasive fungal infections and the associated mortality rate are distinctly high. In one study, for example, the overall incidence of invasive yeast infections was 16.5 cases per 1,000 admissions, and for filamentous fungi, 2.3 cases per 1,000 admissions (1). Although the relative incidence of invasive fungal infection is low, prophylaxis with oral/systemic antifungal agents is a very common indication due to the increasing use immunosuppressants during critical care, cancer chemotherapy and organ transplantation (2, 3). The success of these regimens is driven by effective dosing, with sub-optimal antifungal exposures a risk factor for failure of both prophylaxis and treatment antifungal courses.

Posaconazole is an extended spectrum triazole active against a range of yeasts and molds including *Aspergillus, Candida, Coccidioides, Cryptococcus neoformans, Fusarium, and Zygomycetes* (4). It may be used for the prevention of invasive fungal infections in immunocompromised patients including febrile neutropenic patients and those receiving immunosuppressant drugs for graft-vs-host disease during stem cell transplantation (5). It is also used for treatment of systemic fungal infections (6). The use of oral posaconazole in critically ill patients has been limited to stable patients with intact gut function, to ensure reliable bioavailability from the liquid formulation (7). Low plasma concentrations of the liquid formulation of posaconazole (mean maximum and minimum concentrations of 0.295±0.152 mg/L and 0.086 ±0. 036 mg/L respectively) have been observed, in surgical ICU patients, when administered via nasogastric tube (7). Similar findings were reported in a general ICU
population, whereby a median steady state minimum concentrations of 0.167 mg/L (interquartile range, 0.104-0.340 mg/L) was observed on day 7 of therapy with a 400 mg twice daily regimen(8). Indeed, the absence of other formulations with more reliable bioavailability has meant that oral posaconazole could not be confidently used for severe fungal infections in the critically ill. To address these concerns, a tablet formulation with enhanced bioavailability and an intravenous (IV) formulation were developed and are now in clinical use (9). The IV formulation in particular is considered a very good option in cases of gut dysfunction which is common in critically ill patients and can lead to low posaconazole concentrations of the liquid formulation (10, 11). However, initial pharmacokinetic (PK) investigations of the IV formulation have only been conducted in hematology patients (9), with data in the critically ill lacking at this time.

Specific IV posaconazole PK data is important because critical illness is associated with pathophysiological mediated changes in antifungal PK which can lead to altered dosing requirements (12). Current data obtained mostly using the liquid formulation suggests that the tissue distribution of posaconazole is extensive with a very large volume of distribution owing to its high lipophilicity which of itself typically means that critical illness-led PK changes may not be significant (13). It is highly bound to plasma proteins (98-99%) and therefore may be affected by the presence of hypoalbuminemia which can occur in up to 40% of critically ill patients (14). The major elimination pathway of posaconazole is through biliary excretion (about 77%) of mainly the unchanged parent compound and the rest through renal excretion as a glucuronide conjugate (13, 15). Thus, posaconazole PK is unlikely to be affected in patients with renal impairment including those requiring renal replacement therapy (16, 17). The extent of hepatic metabolism is also limited such that hepatic dysfunction is likely to have little effect on the need...
for dosing adjustment in hepatic impairment, although monitoring plasma concentration is advocated (15, 18).

Given the lack of data to guide use of IV posaconazole, the objective of this study was to describe the PK of a single dose of IV posaconazole in critically ill patients.
RESULTS

Clinical data: Eight patients were enrolled in the study. The clinical and demographic characteristics of the patients are described in Table 1. Seven of the patients were mechanically ventilated at the time of sampling, with three receiving vasopressors. One of the patients required continuous venovenous hemodiafiltration. The single dose of intravenous posaconazole was added as a second agent in the treatment of suspected yeast infection in 4 patients whilst the other four patients had one or two yeasts identified from sterile sites, 3 patients *Candida albicans*, 2 patients *Candida dubliniensis*, 1 patient each for *Candida glabrata* and *Candida parapsilosis*. Over the entire course of treatment of the above suspected/proven fungal infections 6 patients received fluconazole, 3 patients voriconazole, 2 patients caspofungin and 1 patient lipid complex amphotericin (Abelcet®). One of the patients died with multiple organ dysfunction syndrome resulting from a perforated viscous, although this was considered not related to the study drug nor inadequate treatment of the patient’s presumed infection (no fungal pathogen isolated).

PK data: The plasma PK data are described in Table 2. Figure 1 shows the median (interquartile range) a single dose of plasma posaconazole concentrations over a 48-hour period. At 12-hours, the time of usual re-dosing during the loading phase of IV posaconazole therapy, the median (IQR) concentration was 417 (288-672) ng/mL and at 24-hours, the median (IQR) concentration was 239 (217-387) ng/mL.
To the best of our knowledge, this is the first study to describe the PK of IV posaconazole in critically ill patients. We observed highly variable PK parameter estimates with wide interquartile ranges relative to the median value, in particular for Cmax 1702 (1352-2141) ng/mL, AUC0-24 11,612 (9895 – 18,250), AUC0-∞ 17932 (13823 – 27905) ng*h/mL and Vd 529 (352 – 721) L or 6.7 (5.2 -9.4) in L/kg. The coefficients of variation for these PK parameters were 43% (Cmax), 55% (AUC0-24), 72% (AUC0-∞), and 49% (Vd).

The estimated Vd (median, 529 L) is more than double the value described in healthy volunteers (236 L) (19) suggesting that the drug is distributed more extensively into tissue. Given posaconazole is a lipid soluble drug; the increase in Vd could be profound in those patients with large body weight. Indeed the highest Vd in our cohort (989.9 L) was observed for patient number 8 (Table 1) with a body weight of 120 kg (body mass index, 37 kg/m²). However, previous studies with the oral formulations in healthy volunteers and hematology patients did not report significant impact of obesity related increase in volume of distribution on plasma concentrations (20); although the lowest Cmax observed in our study (684 ng/mL, Table 2) corresponds to this patient with highest Vd and body weight (Table 1).

The median Cmax in this study was 1702 ng/mL, which is by far lower than the mean Cmax of 2840 ng/L reported for healthy volunteers by Kersemaekers et al (19). The increase in Vd (529L vs 236 L) could mostly explain the lower Cmax observed here, as the peak concentration is directly affected by Vd (21). However, the observed Cmax (1702 ng/mL) is comparable to that reported by Maertens et al. (9) in patients with hematological malignancy (1590 ng/mL), after
the first two IV doses of 300 mg on day one of treatment. That study showed that accumulation occurs after multiple IV doses achieving higher steady state concentration of 2610 ng/mL on day 14.

Similar accumulation is likely in critically ill patients; however in the current study we have not measured steady-state concentrations to make a direct comparison although the $AUC_{0-\infty}$ is representative of $AUC_{0-24}$ at steady-state (22). The $AUC_{0-\infty}$ in our study (after a single IV dose of 300 mg) was only 52% of the steady-state $AUC_{0-24}$ (34,300 n*h/mL) reported in Maertens et al’s (9) hematology cohort who received IV dose of 300 mg twice on day 1, followed by once daily thereafter. On the other hand, the $AUC_{0-\infty}$ was only about 39% of the $AUC_{0-\infty}$ observed in healthy volunteers after a single IV dose of 300 mg (17,932 vs 46,400 ng*h/mL) (19)). This lower exposure could possibly be due to the relatively higher rate of posaconazole clearance in critically ill patients (16.8 L/h in this study vs 6.9 L/h in healthy volunteers (19)). An additional factor that could have contributed to the observed low concentrations is the profound hypoalbuminemia in the studied critically ill patients. The median albumin concentration was 20 g/L, much lower than normal values for which a normal range is 35 to 55 g/L. Because posaconazole is highly bound to plasma proteins (99 %) (23), the presence of reduced albumin concentrations can affect the extent of protein binding and associated unbound plasma concentrations leading to increased distribution into tissue. This is in line with the elevated $V_d$ we observed (Table 2). Furthermore, the increased free fraction resulting from the reduced albumin concentration means that more drug is available for elimination consistent with the increased drug clearance observed in our patients.
The time course of exposure described by AUC$_{0-24}$ could possibly affect the outcome of therapy given that posaconazole is thought to exhibit both concentration and time dependent antimicrobial activity, which can be described by the ratio of AUC/MIC (24, 25). However, pharmacodynamic studies are limited and inconsistent and as such, the optimal dosing target is yet to be validated in a clinical study (26). Generally higher concentrations appear to increase the likelihood of improved patient outcomes (6, 10, 26, 27). Some guidelines recommend steady state trough concentrations greater than 0.7 µg/mL for prophylaxis and greater than 1 µg/mL for treatment of invasive fungal infections (3). Clearly, more data is required to accurately describe optimal plasma concentration-response relationships as there is inconsistency between studies/authors in the recommended trough concentrations (3, 10, 15). However, it is also apparent that clinical efficacy is well correlated with plasma concentration (10). In previous studies, average steady-state concentrations (Css) between 500 and 2,500 ng/mL, estimated by dividing steady state AUC$_{0-24}$ by 24 h, has been associated with favorable outcomes in clinical trials (9, 28, 29). For the current study, the median Css (747 ng/mL) is within this range, and for only one of the eight patientCss was < 500 ng/mL. The maximum Css was 1555 ng/mL. Therefore, the exposures achieved in the critically ill appear in the lower end of this suggested 500 and 2,500 ng/mL Css range, although the licensed second 300mg dose 12-hours after the first dose, would mean that under dosing is unlikely in the initial phase of treatment. Furthermore, the median Css value (747 ng/mL) is only about half of that recently reported by Cornely et al. (1500ng/L) when given as a prophylactic agent in patients with hematological malignancy (30). These observations suggest significantly different PK of intravenous posaconazole in critically ill patients with invasive fungal infections that perhaps warrants further evaluation in large number of patients.
On the other hand the half-life of posaconazole in this study (median 23 h) is comparable to that observed in healthy volunteers (mean 24.6 h) (19). This observation is consistent with the fact that both clearance and volume of distribution were increased which would result in minimal change in the elimination half-life (i.e. $\lambda_z = CL/Vd$). The important implication of this is that the time to steady-state concentration will be unchanged in the critically ill due to the observed PK alterations, although the steady state concentration will be lower, unless a loading dose regimen is used as is currently recommended for IV posaconazole (i.e. 300mg IV 12-hourly for two doses, then 300mg IV 24-hourly). This is important because multiple doses of intravenous posaconazole infusions are not well tolerated when administered via a peripheral catheter with a high incidence (80%) of infusion site reactions previously reported (19). Such infusion related reactions are, however, minimal with central venous catheters as are used in critically ill patients.

This study is limited by a small sample size of only eight patients. However this is the first study to describe the PK of IV posaconazole from an intensive sampling scheme over 48 h. Another limitation is that, only total plasma concentrations were measured. Given the high plasma protein binding of posaconazole and the possible effect of hypoalbuminemia, further studies should aim to describe unbound posaconazole PK in plasma. Nonetheless, the interpretation of unbound posaconazole concentration remains unclear with limited data available relating total concentration with clinical outcomes. Lastly, the PK analysis was based on the non-compartmental approach, given most previous population PK models described for posaconazole so far were based on one compartment model (31). We recommend further studies based on the population PK approach to describe clinical descriptors of posaconazole exposure that could possibly guide future dosing.
In conclusion, the PK of a single dose of 300 mg IV posaconazole in critically ill patients were different to PK data from Kersemaekers et al (19) in healthy volunteers receiving the same IV dose of 300 mg.
METHODS

This was a prospective, observational PK study, performed in the ICU of a 950-bed teaching hospital. The study was approved by the Royal Brisbane and Women’s Hospital Human Research Ethics Committee (HREC/16/QRBW/377) and the Ethics Committee at The University of Queensland (2016001354). Informed consent was obtained from the patient or the patient’s legally authorized representative.

**Patient selection:** The inclusion criteria were admission to the ICU, age ≥ 18 years, the presence of suspected or confirmed fungal infection requiring systemic antifungal therapy and presence of central venous access for drug administration. The single dose of posaconazole was able to be given as an additional drug to other existing anti-fungal therapy. The exclusion criteria were pregnancy, prescription of drugs that are known to interact with posaconazole as per the product information, use of oral posaconazole within the last two weeks prior to enrolment or a documented history of drug reaction to a triazole antifungal. A decision to prescribe anti-fungal therapy occurred as part of the routine care by the attending clinicians.

**Data collection:** Various patient clinical and demographic data, diagnosis, and microbiology data (pathogen and susceptibility, MIC, where available) were collected. Other data included Acute Physiology and Chronic Health Evaluation II [APACHE II] score on ICU admission (32), Sequential Organ Failure Assessment [SOFA] score (33), presence of shock and mechanical ventilation on days of sampling, renal function (serum creatinine concentrations and measured urinary creatinine clearance, hepatic function markers, concomitant medications and presence of renal replacement therapy (modality and settings used).
Posaconazole administration: In addition to the drugs given as part of the usual care as described above, a single dose of posaconazole was administered for the purposes of this study. 300mg IV posaconazole, diluted with 0.9% sodium chloride or 5% dextrose in water, was administered by slow infusion over 90 minutes through existing central venous access. The drug was infused through a 0.22 micron polyether sulfone (PES) or polyvinylidene difluoride (PVDF) filter.

Sample collection: Serial blood samples (2 mL) were collected in lithium heparin tubes immediately before and after administration of posaconazole. The first sample was collected immediately before commencing the posaconazole infusion with samples collected during the infusion at 15 minutes, 45 minutes, 75 minutes and then 90 minutes (post-infusion), 3h, 5h, 8h, 12h, 18h, 24h, 30h, 36h and 48h after the commencement of drug infusion. The plasma was separated by centrifugation (3000 rpm for 10 minutes) and frozen under -80°C for storage until drug assay.

Posaconazole assay: Total concentrations of posaconazole in plasma were measured by a validated UHPLC-MS/MS method on a Shimadzu Nexera2 UHPLC system coupled to a Shimadzu 8030+ triple quadrupole mass spectrometer. Plasma (10 µL) was spiked with deuterated internal standard ([4H4]-posaconazole) and proteins precipitated with methanol. An aliquot of 2 µL of the supernatant was injected onto the UHPLC-MS/MS. The stationary phase was a C18 Shimadzu Shim-pack XR-ODS III, 1.6 µm column (Shimadzu, Kyoto, Japan) operated at room temperature. The mobile phase A was 10 mM ammonium formate with 0.1% formic acid in water (v/v), and Mobile Phase B was 100% acetonitrile with 0.1% formic acid (v/v). The mobile phase of 40%A and 60%B was delivered isocratically at a flow rate of 0.4
mL/min for 1.8 min run-time and produced a back pressure of about 5600 psi. Posaconazole was monitored by positive mode electrospray at MRM's of 701.35→127.00 (measurement) and 701.35→683.40 (reference). [^H_4]-posaconazole was monitored in positive mode at 705.30→127.20. The assay method was validated using the FDA criteria for bioanalysis from 20 to 5000 ng/mL (34).

**Pharmacokinetic analysis**: The PK parameters for total posaconazole concentrations were estimated using non-compartmental methods. The area under the concentration-time curve from 0-24 hours (AUC_{0-24}) and area under the plasma concentration-time curve from time zero to infinity (AUC_{0-∞}) were calculated using the trapezoidal rule; clearance (CL) = Dose/AUC_{0-∞}. The maximum concentration for the dosing period (C_{max}) and the minimum concentration for the dosing period (C_{min}) were the observed values; apparent terminal elimination rate constant (λ_{z}) was determined from log-linear least squares regression analysis of concentrations from the terminal phase; the apparent volume of distribution (V_d) = CL/λ_z; the half-life (T_{1/2}) = ln(2)/λ_z.

Figures were prepared using Prism® (GraphPad, version 7.0, San Diego California USA).
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### Table 1: Clinical and demographic characteristics of patients

| Patient | Age (yrs) | Gender | Weight (Kg) | BMI | APACHE II Score (admission) | SOFA Day 1 | SOFA Day 2 | Serum creatinine (umol/L) | Urinary creatinine clearance (mL/min) | Serum albumin (g/L) | ALT (IU/mL) | AST (IU/mL) | ALP (IU/mL) | Total bilirubin (umol/L) | INR |
|---------|-----------|--------|-------------|-----|-----------------------------|------------|------------|--------------------------|---------------------------------|------------------|-------------|-------------|-------------|--------------------------|-----|
| 1       | 32        | Female | 65          | 25.4| 17                          | 4          | 2          | 171                      | 34                             | 23               | 57          | 26          | 124         | 11                       | 1.1 |
| 2       | 45        | Male   | 75          | 24.5| 10                          | 3          | 2          | 58                       | 132                            | 28               | 8           | 28          | 63          | 11                       | 1.5 |
| 3       | 41        | Male   | 46          | 17.1| 24                          | 3          | 4          | 84                       | 61                             | 16               | 84          | 126         | 63          | 8                        | 1.2 |
| 4       | 46        | Male   | 65          | 20.7| 17                          | 6          | 4          | 84                       | 103                            | 33               | 58          | 141         | 43          | 45                       | 1.3 |
| 5       | 46        | Male   | 101         | 31.2| 17                          | 6          | 1          | 127                      | 59                             | 22               | 28          | 41          | 84          | 11                       | 1.3 |
| 6       | 58        | Male   | 63.8        | 20.1| 25                          | 6          | 4          | 201                      | 86                             | 18               | 26          | 46          | 65          | 11                       | 1.3 |
| 7       | 60        | Male   | 70.4        | 20.3| 17                          | 2          | 3          | 43                       | 128                            | 18               | 48          | 47          | 368         | 8                        | 1.4 |
| 8       | 49        | Male   | 120         | 37.0| 33                          | 15         | n/a        | 378                      | 0                              | 15               | 66          | 162         | 102         | 194                      | 2.1 |
| Median  | 46        | Female | 68          | 22.6| 17                          | 5          | 3          | 106                      | 74                             | 20               | 53          | 47          | 75          | 11                       | 1.3 |
| 25th centile | 40 | Female | 65 | 20.2 | 17 | 3 | 2 | 78 | 53 | 18 | 28 | 38 | 63 | 10 | 1.3 |
| 75th centile | 51 | Female | 82 | 29.7 | 24 | 6 | 4 | 179 | 109 | 24 | 60 | 130 | 108 | 20 | 1.4 |

Abbreviations – BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; ALT, Alanine transaminase; AST, Aspartate transaminase; ALP, Alkaline phosphatase
Table 2: Estimated posaconazole pharmacokinetic parameters in critically ill patients administered with a single intravenous dose of 300 mg

| Patient | C<sub>max</sub> (ng/mL) | C<sub>min</sub> (ng/mL) | AUC<sub>0-24</sub> (ng.h/mL) | AUC<sub>0-∞</sub> (ng.h^2/mL) | AUMC<sub>0-24</sub> (ng.h^2/mL) | AUMC<sub>0-∞</sub> (ng.h^2/mL) | CL (L/h) | λ<sub>e</sub> (h⁻¹) | T<sub>1/2</sub> (h) | V<sub>d</sub> (L) |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|---------|-----------|--------|-------|
| 1       | 1702            | 92              | 10202           | 10505           | 68898           | 88077           | 28.6    | 0.066     | 10.5   | 432.7 |
| 2       | 1956            | 250             | 15129           | 16996           | 128426          | 258915          | 17.7    | 0.046     | 15.2   | 386.5 |
| 3       | 2699            | 668             | 27692           | 37323           | 261386          | 1020763         | 8.0     | 0.032     | 21.4   | 247.9 |
| 4       | 3187            | 825             | 27614           | 63846           | 274528          | 3283387         | 4.7     | 0.019     | 36.8   | 249.2 |
| 5       | 1703            | 191             | 12071           | 18869           | 114418          | 733394          | 15.9    | 0.023     | 29.8   | 684.6 |
| 6       | 1351            | 229             | 11154           | 14149           | 99393           | 331489          | 21.2    | 0.034     | 20.4   | 625.4 |
| 7       | 1353            | 209             | 8975            | 12847           | 75456           | 398739          | 23.4    | 0.028     | 24.6   | 828.7 |
| 8       | 684             | 220             | 6814            | 24766           | 70537           | 1968464         | 12.1    | 0.012     | 56.6   | 989.9 |
| Median  | 1702            | 224             | 11612           | 17932           | 106905          | 566067          | 16.8    | 0.030     | 23.0   | 529.1 |
| 25<sup>th</sup> centile | 1352 | 196 | 9895 | 13823 | 74226 | 313345 | 11.1 | 0.022 | 19.1 | 352.2 |
| 75<sup>th</sup> centile | 2141 | 563 | 18250 | 27905 | 161665 | 1257689 | 21.7 | 0.037 | 31.6 | 720.6 |

Legend: C<sub>max</sub> – observed maximum concentration during sampling period; C<sub>min</sub>, – observed minimum concentration at 24 hours post dose; AUC<sub>0-24</sub> – area under the concentration-time curve during first 24-hours; AUC<sub>0-∞</sub> – area under the concentration-time curve from 0 to infinity; AUMC<sub>0-24</sub> – area under the moment curve during first 24-hours; AUMC<sub>0-∞</sub> – area under the moment curve from 0 to infinity; CL – clearance; λ<sub>e</sub> – elimination rate constant; T<sub>1/2</sub> – elimination half-life; V<sub>d</sub> – volume of distribution.
Figure 1: Median (IQR) posaconazole concentration vs time data from eight critically ill patients administered with a single intravenous dose of 300 mg.
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