

Pharmacokinetic study of intravenous posaconazole in a critically ill patient with multiple organ failure: A case report

Suthinee Taesotikul¹, Pitchaya Dilokpattanamongkol², Witchit Nosoongnoen², Panadda Panusitthikorn³, and Porpon Rotjanapan⁴

1. Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand
2. Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand
3. Department of Pharmacy, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
4. Division of Infectious Diseases, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

CASE STUDY

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Corresponding Author:

Porpon Rotjanapan, MD

Division of Infectious Diseases, Department of Medicine
Ramathibodi Hospital, Mahidol University
270 Rama VI Road, Ratchatewi, Bangkok 10400, Thailand
Email: porpon.rot@mahidol.ac.th

ABSTRACT

Prescribing antimicrobial therapy in critically ill patients is challenging given lack of standard recommendation. Herein, a pharmacokinetic study of intravenous posaconazole was conducted to confirm plasma and tissue concentrations in a 37-year-old patient with invasive *Aspergillus terreus* infection coincided with renal and hepatic impairment. After dosing adjustment to 300mg every 48 hours, posaconazole exposure using area under the concentration-time curve (AUC) and average concentration (Cavg) reached the target recommendation. However, no significant accumulation of tissue posaconazole was found. Moreover, hyperbilirubinemia may have an influence on posaconazole pharmacokinetics that further studies are needed to explain this phenomenon.

Key Words

Posaconazole, intravenous, pharmacokinetics, critically ill

Implications for Practice:

1. What is known about this subject?

There is no dosage recommendation of intravenous posaconazole in critically ill patients with multiple organ failure.

2. What new information is offered in this case study?

Lower dose of intravenous posaconazole can be applied to the patient with close therapeutic drug monitoring.

3. What are the implications for research, policy, or practice?

Pharmacokinetics of intravenous posaconazole may be changed by liver impairment especially with hyperbilirubinemia and pathologic lung disease.

Background

Posaconazole is a broad spectrum, lipophilic, triazole antifungal agent that has been used as a salvage therapy of invasive mould infections including invasive aspergillosis.^{1,2} Good tissue penetration, non-cytochrome P450 metabolism and no dosage adjustment in renal impairment are considered dominant properties.^{3,4} Based on current knowledge mostly in haematologic malignancy patients not in critically ill individuals, dose adjustment of posaconazole is not necessary in mild hepatic impairment (liver transaminase levels of <3 x upper limit of normal (ULN) and total bilirubin of <2 x ULN).^{1,2,5,6} This study was further conducted based on a previous published case report of invasive *Aspergillus terreus* pulmonary infection with renal and hepatic impairment⁷ to explore a complete pharmacokinetic study of intravenous posaconazole in this particular setting. Tissue concentrations were also

investigated to examine correlation of plasma and tissue drug concentrations.

Case details

A 37-year-old male patient (actual body weight, 86kg; height, 1.85m; body mass index, 25kg/m²) was diagnosed of dengue haemorrhagic fever with acute respiratory distress syndrome, haemophagocytosis syndrome, and multiple organ failure secondary to circulatory shock. After first month of admission, *A. terreus* grew from tracheal suction specimens and bronchoalveolar lavage fluid that confirmed additional diagnosis of invasive pulmonary aspergillosis. Minimal inhibitory concentrations of the pathogen to posaconazole, voriconazole, anidulafungin and micafungin were 0.125, 0.75, 0.004 and 0.064mg/L, respectively. After 10-day course of intravenous and nebulized voriconazole combined with oral flucytosine, worsened respiratory status was documented described as need of full respiratory support, progression of pulmonary lesions on serial chest radiographs and increment of serum galactomannan in spite of therapeutic voriconazole concentrations of 3.29 to 4.89mg/L. His liver function tests were elevated since admission with median alanine transferase (ALT) of 223 units/L and mean total bilirubin (TB) of 22.38+10.45mg/dL. Concerns of possible treatment failure and potential further hepatotoxicity were raised. Posaconazole in combination with micafungin became the next option of treatment. Through the treatment course, ventilator support, intercostal drainage and continuous venovenous haemodiafiltration (CVVHDF) were applied for consequences of complication after dengue haemorrhagic shock and continued until his death. The CVVHDF prescription during posaconazole therapy comprised of ultrafiltration rate of 1,600mL/h with blood flow rate of 180 mL/min. Posaconazole dosage regimen and plasma concentrations are presented in Figure 1.

Chronological posaconazole dosage adjustment

Phase I: Conventional dosage regimen

Intravenous posaconazole was initiated on hospital day 38 at the dose of 300mg via central venous catheter over 90 minutes every 12 hours in the first day, followed by 300mg every 24 hours on hospital days 39–49. After 7 days of therapy which was assumed to have reached steady state⁸, trough plasma posaconazole concentration was above 3mg/L which was higher than target concentration of >1.0mg/L.⁹ However, trough plasma posaconazole continued to rise following the course of treatment to greater than 4mg/L that exceeded upper limit threshold of 3.65mg/L.¹⁰ The maximal concentration that ever reported was as high as 10.1mg/L and that created visual

hallucination and neurological disturbance.¹¹ Besides, little is known regarding possibility of dose-related toxicity, potential worsening liver impairment and QT prolongation on electrocardiography and these became considerations.¹² Therefore, intensive care team decided to withhold next doses of posaconazole and considered redosing when plasma concentration declined to 1mg/dL or below.

Phase II: Modified dosage regimen

Plasma drug concentration slowly diminished to 1mg/L in 120 hours following withdrawal of the agent and 300mg of intravenous posaconazole was resumed with a watchful plan to determine an appropriate interval. Eventually, 300mg of posaconazole every 48 hours was justified as the final regimen until his death. Additional dose of 300 mg posaconazole was also administered in case of excessive blood loss >1500mL from any surgical procedures¹³ which is shown in Figure 1.

During posaconazole treatment, median ALT had downward trend to 121IU/L whilst TB levels showed no significant change by the mean of 19.57±3.42mg/dL. No interaction between posaconazole and enzyme-inducing or enzyme-inhibiting drugs (phenytoin, rifampin, cimetidine) was observed during the treatment.

Pharmacokinetic analysis

Blood sampling and analysis¹⁴

When the steady state of 300mg posaconazole every 48 hours was achieved, pharmacokinetic parameters and posaconazole exposure were calculated from multiple plasma drug concentrations during 1 dose administration. Blood samplings were collected in heparin tube on day 15 after extending dosing interval at pre-dose (0 hours), immediately the end of infusion (1.5 hours) and post-doses (2, 3, 18, 30 and 48 hours). In Figure 2, posaconazole concentration apparently demonstrated the 2-compartment kinetics consisted of the alpha phase (distribution) and the beta phase (elimination). This pattern described that posaconazole can distribute to peripheral and central compartments of human's body. Thus, 2-compartment infusion model was appropriate pharmacokinetic design to compute the pharmacokinetic parameters with WinNonLin 6.3 the software Phoenix Build 6.3.0, (Certara, St. Louis, MO). Posaconazole exposure was also calculated as AUC by trapezoidal rule.

Tissue sampling and analysis

Pulmonary tissue drug concentration was determined soon after left pneumonectomy and that was 9 days of conventional dosing regimen of posaconazole treatment.

Tissue samplings from various sites were also pursued including right lung, liver, kidney and heart right after his death at autopsy for tissue drug concentration determination.¹⁵

Until analysed, blood and tissue samples were immediately stored at -20°C and -80°C, respectively. Plasma and tissue supernatants were assayed by using a validated Ultra Performance Liquid Chromatography-Photo Diode Array (UPLC/PDA), according to the US Food and Drug Administration guidance for bio-analytical method validation.¹⁶

Results

Pharmacokinetic parameters of posaconazole are exhibited in Table 1 in comparison with previous 4 pharmacokinetic studies. Ratio of the area under the concentration time curve at 48 hours to the minimum inhibitory concentration (AUC/MIC) of *A. terreus* was 579 in this patient. Plasma and pulmonary tissue posaconazole concentrations are demonstrated in Table 2 and tissue posaconazole concentrations at different sites are displayed in Table 3.

Discussion

Intravenous posaconazole has been developed to ensure 100 per cent bioavailability which is more preferable in critically ill patients who mostly have gastrointestinal intolerance, drug interaction with acid suppressant, and unplanned refraining of enteral feeding which could potentially interfere drug absorption.⁸ Mostly dose recommendations are referred to clinical studies in either healthy volunteers or patients with minor organ dysfunction but there have been no studies conducting in more severe organ dysfunction particularly renal and hepatic impairment.^{5,17} Similarly to this case study, posaconazole dosing regimen was adjusted to 300mg every 48 hours with therapeutic drug monitoring implemented.

In comparison of pharmacokinetic study of a single dose of intravenous posaconazole in healthy volunteers⁵ and in a critically ill patient undergoing continuous veno-venous haemofiltration (CVVH)¹⁸, this study's regimen yielded the similar elimination rate constant (K_e) sharing the same pharmacokinetic character of posaconazole but drug clearance was much lower in the present study. Generally, posaconazole is metabolised by UDP-glucuronosyl transferase (UGT) 1A4 to more hydrophilic and inactive metabolite.⁴ The diminished UGT activity can suppress metabolism of posaconazole to posaconazole-glucuronide, resulting in an increase of plasma posaconazole concentration. Bilirubin has long been described to be an

inhibitor of UGT1A4 from *in vitro* study.¹⁹ The presence of 100µmol/L bilirubin concentration in human liver microsome was able to inhibit UGT1A4 activity by 63.5 per cent and there was a trend of further inhibition effect at higher level of bilirubin concentration. Moreover, severity of hepatic inflammation was correlated with reduction of glucuronidation activity measuring by expression of UGT mRNA, including UGT1A4.¹⁹ This correlation was not found in fibrotic condition or chronic liver disease.²⁰ For this patient, not only persistent hyperbilirubinemia but also findings of liver congestion, haemochromatosis, and acute to chronic hepatitis without fibrotic or cirrhotic changes in autopsy potentially influenced posaconazole metabolism as well. Therefore, we postulated that the inhibitory effect of bilirubin on glucuronidation combined with ongoing inflammatory process might diminish posaconazole clearance resulting in higher plasma posaconazole concentrations than anticipated while on conventional dosage regimen.⁵

Regarding antifungal efficacy, Cavg was still measured above 1.0mg/L as recommendation for salvage therapy of invasive fungal disease in this patient.⁹ Even supratherapeutic trough level was not reached 1.8mg/L as suggested by Dekkers et al., his plasma AUC/MIC ratio had been warranted by value of more than 200.⁸ Study in murine model from Howard et al. indicated that the AUC/MIC of 441 resulted in 90 per cent of the maximal antifungal effect²¹ which may imply adequate drug exposure in the case study.

Fundamentally, posaconazole is able to diffuse extensively to various organ systems given physiochemical property of high lipophilicity²² and pharmacokinetic properties of large volume of distribution with prolonged elimination half-life.⁴ These characteristics promote drug penetration to pulmonary epithelial cells and pulmonary macrophages which are host cells for defending invasive pulmonary aspergillosis.²³ Evidences of cellular accumulation in pulmonary epithelial cells and macrophages were demonstrated in *in vivo*, animal and human studies^{15,24,25} representing as a ratio of tissue and plasma concentration ≥ 1 .²² However these findings were not detected in this case study as the mentioned ratio was less than 1 during the study period. This may imply poor tissue posaconazole distribution as well as no cellular accumulation observed. There was no clear explanation on this phenomenon but tissue pathology may be the clue. Due to multiple organ failure from poor tissue perfusion and progressive respiratory failure with haemothorax during admission, autopsy revealed necrotic, haemorrhagic and fibrotic

changes of the remaining lung tissue turning to end stage lung disease. Hepatocytes were also with degenerative changes and turned to necrosis and fibrosis. These may be the reason to explain unexpected less drug accumulation in injured pulmonary tissue despite of therapeutic plasma concentrations.

Furthermore, the results revealed less pulmonary tissue posaconazole concentration in upper lobe compared to lower lobe. The postulation was by the fact that higher pulmonary blood flow is generally documented in lower lung field and lesser proportion of blood flow to the upper part.^{26,27} Other possible explanation was elevated alveolar pressure in upper lung zone exceeds pulmonary arterial pressure causing lower drug penetration into the area. Besides these, we demonstrated that posaconazole distributed best into the hepatic tissue similarly to previous study.¹⁵

Regarding a concern of accumulation of sulfobutylether- β -cyclodextrin (SBECD), the solubilising agent in injection formulation with potential of further renal function deterioration in animal model,²⁸ avoidance of intravenous posaconazole was stated for individuals who had creatinine clearance of <50mL/min.²⁹ However, SBECD in posaconazole was completely removed by CVVH according to a report from Morris et al.¹⁸ In addition, no renal tubular vacuolation, which found after multiple dose of SBECD in rats model,²⁸ was presented in final autopsy report. Therefore, intravenous posaconazole gained more benefit in patients receiving CVVH in this aspect. Infusion-related reaction, QT prolongation on electrocardiography and progressive liver impairment were not detected in this patient.⁷

This study presents several limitations that restrict general application to different individuals as follows: (i) This is the pharmacokinetic study in a single critically ill patient with changes in physiologic variabilities and extremes of organ dysfunction. (ii) Instability of patient's condition did not allow a longer period of time in analysing pharmacokinetic data. (iii) Lack of formal inspection of the influence of CVVHDF on plasma drug concentration despite the prediction that posaconazole should not be obviously removed via renal replacement therapy based on its high molecular weight (700.8g/mol), high degree of plasma protein binding (98 per cent), and large volume of distribution.⁴ (iv) The outcome of tissue posaconazole penetration was abundantly different from prior studies which could be explained by degrees of pathologic changes in each organ system. However, drug concentrations in

damaged tissue were much lower than in normal ones in which a study in depth to explain this circumstance was not included in this report.

Conclusion

This study exhibited that favourable posaconazole exposure (AUC, C_{avg}) in a single critically ill patient with hepatic impairment and hyperbilirubinemia can be achieved with dosing reduction regimen to 300mg every 48 hours of posaconazole although desired tissue concentrations were not commenced. However, plasma therapeutic drug monitoring remains a standard of care and crucial for real-life clinical practice to ensure optimum clinical efficacy. Further clinical studies at a larger scale are needed to explore the real posaconazole pharmacokinetics in multiple organ failure individuals.

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PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

ETHICS COMMITTEE APPROVAL

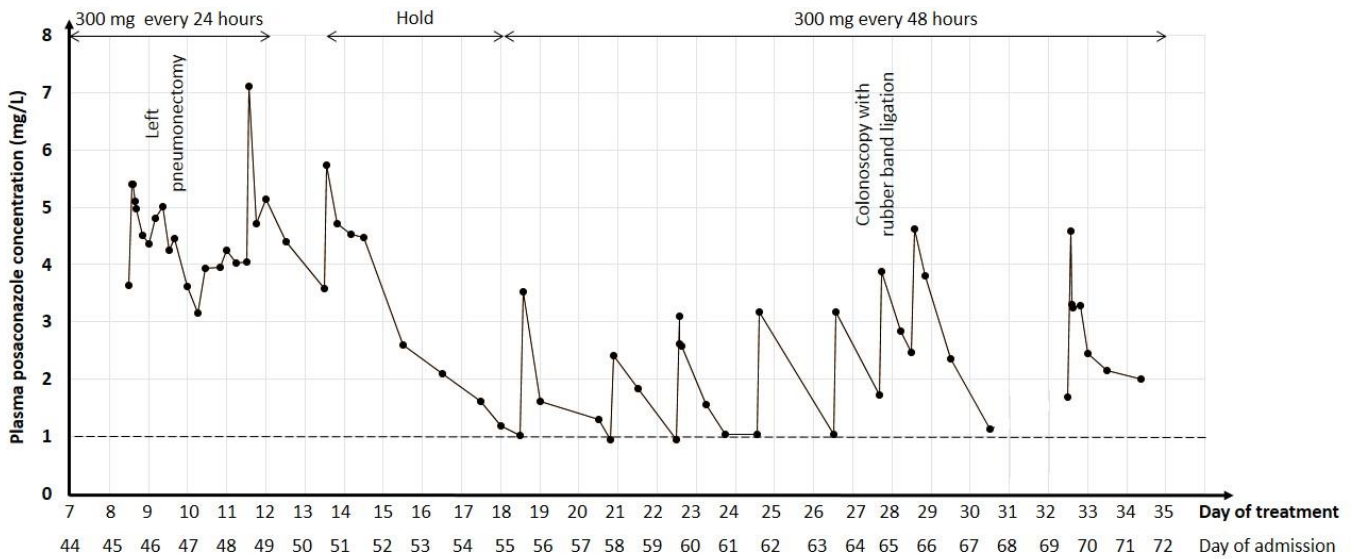
The study has been previously approved by Ethics Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University, at 28 December 2015. Ethical Number: MURA2015/767.

PATIENT CONSENT

The authors, *Taesotikul S, Dilokpattanamongkol P, Nosoongnoen W, Panusitthikorn P, Rotjanapan P*, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient in this report.
2. All possible steps have been taken to safeguard the identity of the patient.
3. This submission is compliant with the requirements of local research ethics committees.

Figure 1: Plasma posaconazole concentrations during course of treatment with dosage adjustment to maintain concentration above 1.0mg/L (dotted line)



Intravenous posaconazole 300 mg every 12 hours was initially administered in the first day of treatment, followed by 300mg every 24 hours as recommendation for 12 days. During days 12–14 of treatment, dosing interval was extended to 48 hours and eventually resumed the dose at 120 hours to allow plasma drug concentration to descend to 1mg/L range. Thereafter, 300mg of posaconazole every 48 hours was commenced until his death on day 34 of treatment or day 71 of admission. On day 27 of posaconazole, another 300mg of posaconazole was added in response to massive gastrointestinal bleeding necessitating blood transfusion.

Figure 2: Posaconazole concentrations in plasma using 300mg of intravenous posaconazole every 48 hours on day 22 of treatment course or day 15 after extending dosing interval. Solid line represents the observed plasma concentrations and dotted line represents the predicted plasma concentrations using 2-compartment model

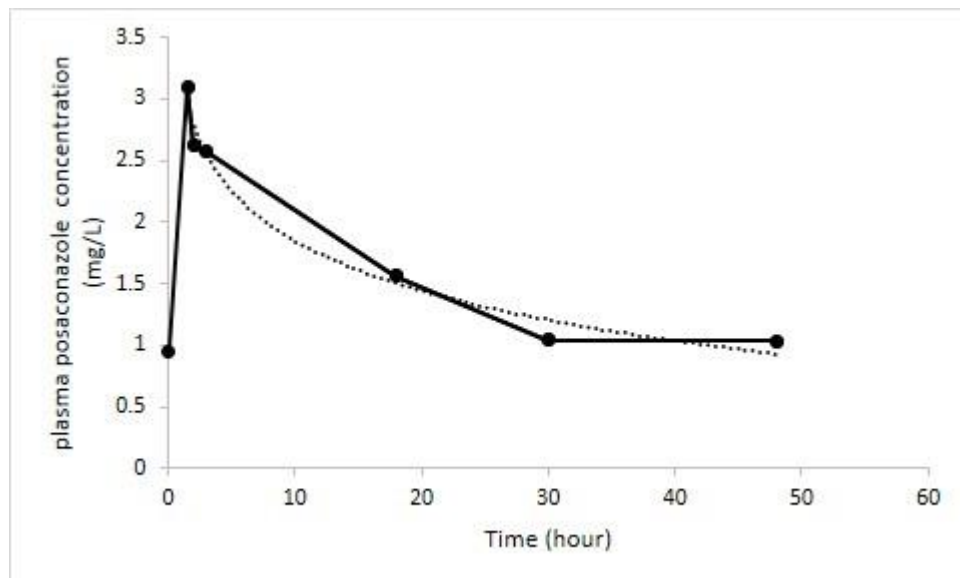


Table 1: Pharmacokinetic parameter values

Pharmacokinetic parameter	Case	9 healthy volunteers ¹⁷	19 patients with haematologic malignancy ⁵	49 patients with haematologic malignancy ³⁰	1 patient with CVVH ¹⁸
Dose	300mg/48 h	300mg single IV	300mg/24 h	300mg/24 h	300mg/24 h
t _{1/2} (h)	27.07	24.6	NA	NA	31
Ke (h ⁻¹)	0.0256	0.0292	NA	NA	0.0222
CL (L/h)	2.29	6.9	NA	NA	9.5
AUC (ng·h/mL)	72,386 [*]	45,500 [†]	34,300 [‡]	36,100 [‡]	53,000 [‡]
Cavg (mg/L)	1.51	NA	1.43	1.50	2.21

T_{1/2}: half-life, Ke: elimination rate constant, CL: posaconazole clearance, AUC; area under the curve, Cavg: average posaconazole concentration

*AUC_{0-48h}

† AUC_{0 to ∞}

Table 2: Pulmonary tissue and plasma posaconazole concentrations and time interval of plasma and tissue samplings

Patients	Tissue concentration (ng/g)	Plasma concentration (ng/mL)	Ratio of tissue/plasma concentration	Time from last plasma sampling to tissue sampling [§] (day)	Time from last dose to tissue sampling [§] (h)
Case	1,304.4 (left lower lobe)**	4,365	0.28	0	24
	66.4 (left upper lobe)**		0.01	0	24
	1,632 (right lobe)***	2,015	0.89	2	50
Patient 1*	140	30	4.67	2	81
Patient 2*	200	10	20	1	16
Patient 3*	110	40	2.75	0	65
Patient 4*	550	70	7.86	0	24
Patient 5*	670	50	13.4	4	79
Patient 6*	4,530	330	13.73	3	58
Patient 7*	890	390	2.28	0	19

*Data from Blennow et al.¹⁵

**tissue concentrations on day 8 of posaconazole treatment

***tissue concentration on day 34 of posaconazole treatment

§The authors assumed tissue sampling in patients # 1–7 were performed at their death

Table 3: Posaconazole tissue concentrations at different sites

Patient	Plasma concentration (ng/mL)	Tissue concentration (ng/g)			
		Kidney	Liver	Heart	Lung
Case	2,015	880	1,384	594	1,632
Patient 1*	30	480	620	310	140
Patient 2*	10	320	660	180	200
Patient 3*	40	280	260	Not determined	110
Patient 4*	70	510	1,000	510	550
Patient 5*	50	330	500	260	670
Patient 6*	330	4,600	7,460	1,790	4.530
Patient 7*	390	1,550	2,260	1,730	890

*Data from Blennow et al.¹⁵