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Pharmacokinetics and tolerability of intravenous posaconazole in healthy Chinese volunteers: a randomized, open-label and single-dose study

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Posaconazole is a triazole antifungal drug with strong antifungal effect. The pharmacokinetics, safety, and tolerability were evaluated following the intravenous administration of posaconazole injection. A total of 36 healthy adults were enrolled in the parallel-designed clinical trial, and the subjects received single doses of posaconazole injection (100, 200 and 300 mg). Posaconazole concentrations in plasma were determined with liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The levels of posaconazole in plasma increased proportionally between 100 and 300-mg dose, but AUC showed a more-than-dose-proportional increase. Besides, decreased *Vd* and *CL* were observed, along with the increased posaconazole dosage. Posaconazole was well tolerated at all dose levels, and the adverse events were not dose dependent. No clinically significant changes in electrocardiograms were observed.

1. Introduction

Posaconazole (Fig. 1), is a second generation triazole broad-spectrum antifungal drug, with strong antifungal activity, good safety and tolerance (Chen et al. 2020; Courtney et al. 2003; Sansone-Parsons et al. 2007; Liu et al. 2020). In 2006, FDA approved posaconazole oral suspension for the prevention of invasive aspergillosis, candidiasis and oropharyngeal candidiasis (OPC). In 2014, FDA approved posaconazole injection (16.7 ml: 0.3 g) for the treatment of high-risk patients infected with invasive *Aspergillus* and *Candida* due to severe immune deficiency.

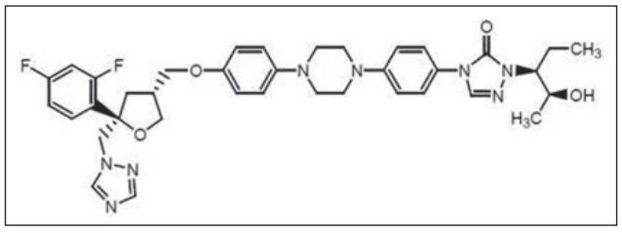

Fig. 1: Chemical structure of posaconazole.

Posaconazole is a highly permeable drug and classified as a Biopharmaceutics Classification System (BCS) class II compound. The bioavailability of posaconazole oral suspension is highly dependent on gastric conditions and will be significantly enhanced when co-administered with food, particularly a high-fat meal (Kraft et al. 2014; Krishna et al. 2009; Li et al. 2017). In fed state, the time to reach maximum plasma concentration (T_{max}) is prolonged and the exposure level parameters (C_{max} and *AUC*) are increased significantly compared with those in fast state (Li et al. 2017). Posaconazole is a strong inhibitor of CYP3A4 and is metabolized primarily in the liver through UDP-glucuronosyltransferase enzyme pathways. After oral administration, posaconazole is excreted primarily through fecal excretion (77%) (Vuletić et al. 2019), and its metabolites eliminated through urine and feces account for only a small amount (17%) of the total dose (Krieter et al. 2004).

Given the possible value for this medication and lack of detailed data reported for the pharmacokinetics and tolerability, a comprehensive pharmacokinetic study on posaconazole injection after single-dose (100 mg, 200 mg and 300 mg) intravenous injection was designed and performed to illustrate posaconazole pharmacokinetic properties and safety characteristics.

2. Investigations and results

2.1. Study design

The study was performed in a accordance with the Good Clinical Practice (GCP) guidelines of NMPA and the Declaration of Helsinki. The study protocol was approved by the independent ethics committee of Jinan Central Hospital (Jinan, China). All subjects provided written informed consent before undergoing any study procedures.

2.2. Subjects

Thirty-six healthy subjects aged 18 to 45 years with a body mass index between 19 and 26 kg/[m]^2 were eligible to participate in this study. Their health was confirmed based on medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and routine clinical laboratory tests. Subjects who were tested positive for the HIV, syphilis, hepatitis B or hepatitis C virus were excluded. All subjects had to have negative findings on screening for drugs (morphine, amphetamine, cocaine, benzodiazepine and *Cannabis sativa*) with commercial kits.

2.3. Pharmacokinetic and statistical analysis

Mean concentrations were obtained and the pharmacokinetic parameters as the elimination half-life $t_{1/2}$, the area under curve *AUC*, the clearance *CL*, the apparent volume of distribution *Vd* and the mean residence time (*MRT*) were calculated with Phoenix WinNonlin software (version 8.1). The maximum plasma concentration C_{max} and the corresponding time to reach maximum plasma concentration T_{max} were observed. Means and standard deviations (SD) were calculated for all pharmacokinetic parameters. Power function model was applicated in the dose proportion analysis.

2.4. Results

2.4.1. Demographic data of subjects

Thirty-six subjects were included in the study and two subjects discontinued treatment for personal reasons, one in the 100-mg group and another in the 200-mg group. There was no difference in subject age and BMI between 100-mg, 200-mg and 300-mg treatment group. No protocol amendments or major protocol deviations were reported. The study demographics are presented in Table 1.

Table 1: Demographic information of the volunteers (x±sd)

Parameters	Dosage		
	100 mg (n=11)	200 mg (n=12)	300 mg (n=12)
Age (yr)	28.9 ± 7.27	27.1 ± 7.40	24.5 ± 5.00
Weight (kg)	60.21 ± 10.458	62.39 ± 8.746	61.03±7.549
Height (cm)	164.95 ± 10.172	165.33 ± 8.630	164.21 ± 8.877

2.4.2. Pharmacokinetics profile

Posaconazole in plasma samples were assayed using a validated liquid chromatography with tandem mass spectrometric detection method. The discontinued subject in the 200-mg group received the administration of 200-mg posaconazole injection, but withdrew from the trial at the fourth day after administration. Therefore, some primary parameters could be obtained for pharmacokinetic analysis. Therefore, the pharmacokinetic analysis finally included the data for 35 subjects. The mean posaconazole concentration-time profiles at each dose level are shown in Fig. 2. The pharmacokinetic parameters were analysed with WinNonlin software and listed in Table 2.

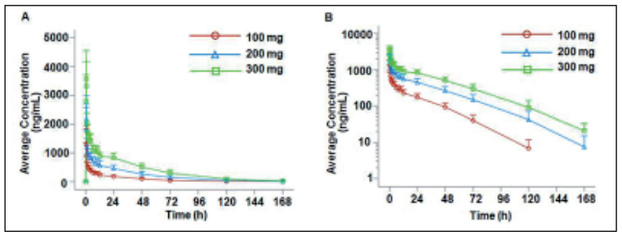

Fig. 2: Mean concentration-time curve for posaconazole in plasma at 100-mg (n=11), 200-mg (n=12) and 300-mg (n=12) level. (A: Raw data, B: Semilogarithmic conversion data).

Table 2: Pharmacokinetic parameters for posaconazole in plasma after administration with a single dose (average, min - max)

Parameters	100 mg (n=11)	200 mg (n=12)	300 mg (n=12)
C_{max} (ng/mL)	1416.00 (572 – 2340)	2252.50 (1320 – 3300)	3738.33 (2290 – 4760)
AUC_{0-t} (ng·h/mL)	12878.76 (8634.02 – 19094.26)	36138.87 (21556.99 – 52092.50)	64715.13 (44622.74 – 92650.65)
$AUC_{0-\infty}$ (ng·h/mL)	13239.26 (9004.86 – 19657.55)	36585.58 (21807.02 – 52995.41)	65523.95 (44922.44 – 94817.79)
T_{max} (h)	0.44 (0.32 – 0.5)	0.43 (0.33 – 0.5)	0.36 (0.17 – 0.52)
$t_{1/2z}$ (h)	20.61 (13.91 – 26.64)	23.32 (18.38 – 31.30)	24.88 (20.27 – 31.89)
V_z (L)	236.65 (148.26 – 426.76)	190.33 (126.43 – 293.87)	168.66 (116.44 – 217.31)
CL_z (L/h)	7.99 (5.09 – 11.11)	5.81 (3.77 – 9.17)	4.78 (3.16 – 6.68)
MRT_{0-t} (h)	25.14 (16.94 – 31.39)	33.52 (23.48 – 41.72)	37.69 (32.77– 46.54)

2.4.3. Pharmacokinetics linear analysis

After administration, the mean posaconazole parameters ranged from 1,416 to 3,738 ng/ml for C_{max}, 12878.76 to 64715.13 h·ng/mL for AUC_{0-t} and 13239.26 to 65523.95 h·ng/mL for $AUC_{0-\infty}$ at doses from 100 to 300 mg. A power function model was used to analysis the relation between dosage and the pharmacokinetic parameters (Fig. 3), and 95% confidence internal of dose-proportionality slope estimation are listed in Table 3. The plasma posaconazole C_{max} increased proportionally between the 100- and 300-mg dose. However, the plasma posaconazole AUC_{0-t} and $AUC_{0-\infty}$ increased proportionally only between the 200- and 300-mg group, and showed a more-than-dose-proportional increase in the scope of 100 to 200 mg.

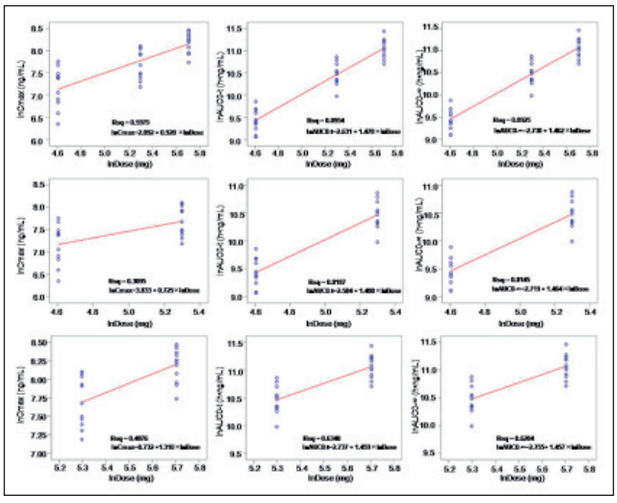

Fig. 3: Linear analysis of posaconazole pharmacokinetics between 100- to 300- mg dosage. (A: 100 mg - 300 mg; B: 100 mg - 200 mg; C: 200 mg - 300 mg.

Table 3: 95% Confidence internal of dose-proportionality slope estimation

Parameters		Estimation	95%CI	*p*-value
C_{max}	100 mg – 300 mg	0.920	0.653~1.188	<0.001
	100 mg – 200 mg	0.725	0.233~1.216	0.006
	200 mg – 300 mg	1.310	0.716~1.903	<0.001
AUC_{0-t}	100 mg – 300 mg	1.478	1.296~1.660	<0.001
	100 mg – 200 mg	1.488	1.161~1.814	<0.001
	200 mg – 300 mg	1.459	0.956~1.962	<0.001
$AUC_{0-\infty}$	100 mg – 300 mg	1.462	1.279~1.645	<0.001
	100 mg – 200 mg	1.464	1.138~1.790	<0.001
	200 mg – 300 mg	1.457	0.949~1.966	<0.001

2.4.4. Safety and tolerance

During the study, 11 adverse events (AEs) were reported, including positive urine leucocytes, positive urine red blood cells, dizziness, nausea, bellyache, diarrhea, vomit, upper respiratory tract infection and hidrosis. Among them, dizziness, nausea, bellyache, diarrhea, vomit and hidrosis were judged to be possibly related to the test drug. All AEs were mild or moderate in severity and not serious. Subjects with AEs were followed up and all contactable subjects were confirmed to have fully recovered.

3. Discussion

Posaconazole is an extended-spectrum triazole with demonstrated efficacy as prophylaxis for invasive fungal disease (IFD) and as treatment for refractory IFD. Compared with the data reported before, the parameters C_{max} and $AUC_{0-\infty}$ in our work were similar in the 100 and 200 mg groups, but higher in the 300 mg group. In this study, posaconazole displayed dose-proportional (C_{max}) pharmacokinetics in the scope of 100 to 300 mg dosage. However, *AUC* parameters did not show dose-proportionality. A single-dose of 100 to 300 mg posaconazole administered intravenously generated a mean C_{max} range of 1,416 to 3,738 ng/ml, a mean AUC_{0-t}

range of 12,878.76 to 64,715.13 ng·h/ml and mean $AUC_{0-\infty}$ range of 13,239.26 to 65,523.95 ng·h/ml. The dose-proportionality slope estimates (95% confidence interval) were 0.920 (0.653 to 1.188) for C_{max}, 1.478 (1.296 to 1.660) for AUC_{0-t} and 1.462 (1.279 to 1.645) for $AUC_{0-\infty}$. Parameters $AUC_{0-\infty}$ indicated a more-than-dose-proportional increase. Furthermore, our data indicated decreased *Vd* (236.65 – 168.66 L) and *CL* (7.99 – 4.78 L/h) from 100 mg to 300 mg dosage, which were less than those reported before (Kersemaekers et al. 2015). ANOVE analysis results of the two parameters showed a statistic difference between the three groups, and individual difference may be the major reason.

In the current study, the pharmacokinetics, safety, and tolerability of oral posaconazole in humans were evaluated, following the administration of increasing single doses. All AEs were mild or moderate in severity and all participants fully recovered during the post-study period.

4. Experimental

4.1. Procedures

This study was designed as a randomized, open-label, single oral dose, parallel trial. 36 healthy subjects were randomized into 100, 200 or 300-mg dose groups (n=12 per group, half male and half female). In each group, subjects received posaconazole intravenous drip (Simcere Pharmaceutical, Jiangsu, China) for 30 min. Blood samples (3 ml) for posaconazole PK evaluation were drawn before (0 h) and 10 min, 20 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h (day 2), 48 h (day 3), 72 h (day 4), 120 h (day 6), and 168 h (day 8) after the beginning of intravenous drip. The blood samples were placed in K_2EDTA-containing tubes and were centrifuged at 1,700 g for 10 min at 4 °C. The plasma was stored at -60 °C until analyzed.

4.2. Bioanalytical methods

The concentration of posaconazole in plasma was determined by a LC-MS/MS method. Plasma (50 µL) was employed and mixed with 50 µL of stable-labeled internal standard. The sample was processed by the method of protein precipitation and 5 µL supernatant was injected onto the autosampler for analysis on API4000. The calibration curve was linear over the plasma concentration range of 5.00-5000 ng/mL. This bioanalytical method including LLQO, linearity, matrix effect, specificity, recovery, stability was fully validated following the bioanalytical method validation guidance from China NMPA.

4.3. Safety and tolerance

Safety was monitored through AEs, physical examinations, vital signs, 12-lead-ECGs, and routine clinical laboratory tests. Information on the AEs, including the type, number, frequency and severity of the AEs, along with relation to treatment, was collected and summarized using descriptive statistics.

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Conflicts of interest: None declared.

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