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ORIGINAL RESEARCH

Effects of Voriconazole on the Safety, Pharmacokinetics and Pharmacodynamics of Ciprofol (HSK3486), a Novel Intravenous Anaesthetic, in Healthy Participants: A Prospective, Randomized, Crossover Clinical Trial

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Purpose: Ciprofol, a novel intravenous anaesthetic, is an analogue of propofol with superior anaesthetic efficacy. Ciprofol is widely metabolized in humans, and cytochrome P450 enzymes (CYPs) are involved in its metabolism. However, the drug–drug interactions between ciprofol and drugs that may affect CYPs remains unclear. Therefore, we investigated the effects of voriconazole on the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ciprofol.

Methods: A randomized, two-period, two-sequence, crossover study was conducted in healthy participants who received a single intravenous dose of 0.4 mg/kg ciprofol (treatment A) and 0.4 mg/kg ciprofol after multiple doses of voriconazole (treatment B), a multiple inhibitor of CYP3A4/5, CYP2B6 and CYP2C9/19, in either sequence AB or sequence BA.

Results: MOAA/S-time curves revealed that the participants were anaesthetized rapidly (2.01 min versus 1.82 min) and recovered smoothly (11.58 min versus 11.64 min) after receiving ciprofol either alone or combined with voriconazole. The mean BIS_{peak} values were 41.1 and 44.4, respectively. Voriconazole slightly increased the plasma AUC of ciprofol, but the 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of plasma ciprofol were still in the range of 80%-125%, which demonstrated pharmacokinetic bioequivalence between the two treatments. No serious adverse effects were reported.

Conclusion: Ciprofol was well tolerated in combination with voriconazole, and the anaesthetic effect was satisfactory. The dose of ciprofol is suggested not be adjusted in patients receiving the CYP inhibitor voriconazole based on the PK, PD and safety characteristics.

Trial Registration: Clinicaltrials.gov, NCT04145583, registered on 25 October 2019.

Keywords: ciprofol, intravenous anaesthetic, drug-drug interaction, pharmacokinetics, pharmacodynamics, safety

Introduction

Ciprofol is a novel intravenous anaesthetic that has been approved for sedation, induction and maintenance of anaesthesia in China. As a structural derivative of propofol, ciprofol introduces cyclopropyl groups to form a chiral centre in its chemical structure.[1,2] The chiral centre of ciprofol gives it a strong affinity for γ-amino butyric acid type A ($GABA_A$)

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receptors, which prolongs the opening of central chloride ion channels and subsequently inhibits the depolarization of postsynaptic neuronal membranes, leading to hypnosis and sedation.[3–5] Ciprofol has a rapid onset of action, with an anaesthetic efficacy that is 4–5 times greater than that of propofol.[6,7] Previous studies also revealed that the incidence of respiratory–related adverse events (respiratory depression, apnoea, and hypoxia), and the proportion of patients requiring assisted ventilation after ciprofol administration were lower than those of patients receiving propofol. The injection pain of ciprofol was also less severe than that of propofol.[1,6–13]

Ciprofol is widely metabolized in humans, primarily mediated by cytochrome P450 enzymes (CYPs) and uridine diphosphate glucuronosyltransferase enzymes (UGTs).[4,14] Previous studies have shown that CYP2B6 is the main CYP isoform mediating ciprofol metabolism, while CYP1A2, CYP2C9/19 and CYP3A4/5 also contribute to its phase I metabolism. Additionally, UGT1A9 serves as the major UGT isoform responsible for its phase II metabolism.[15] Previous clinical drug-drug interaction (DDI) trials have shown that ciprofol does not undergo significant pharmacokinetic change when co-administered with rifampin (a CYP2B6 and UGT1A9 inducer), mefenamic acid (a UGT1A9 inhibitor) or sodium divalproex (a CYP2C9 and UGT1A9 inhibitor).[15–17] However, the DDI between ciprofol and voriconazole remains unclear. Voriconazole is an inhibitor of CYPs and is widely used in DDI studies. Voriconazole inhibits the activity of CYP3A4/5, CYP2B6 and CYP2C9/19, and is recommended for drug interaction studies of the drugs metabolized by these enzymes.[18,19]

This study aimed to investigate the effects of the CYP inhibitor voriconazole on the pharmacokinetics (PK), pharmacodynamics (PD) and safety of ciprofol. This study may also extend DDI findings of ciprofol and provide suggestions for dose adjustment when ciprofol is combined with CYP3A4/5, CYP2B6 and CYP2C9/19 inhibitors.

Methods

This was a single-center, open-label, randomized, two-period, two-sequence, crossover study conducted at the First Affiliated Hospital of Soochow University (Suzhou, China). The study protocol was approved by the Medical Ethics Committee of the First Affiliated Hospital of Soochow University (Ethics Number: 2019169) and conducted in compliance with the Declaration of Helsinki. This trial was registered at ClinicalTrials.gov (NCT04145583). All participants provided written informed consent.

Participants

All the participants were fully informed and provided signed informed consent. Within a two-week screening period, participants aged 18 to 45 years with a body mass index (BMI) between 19 and 26 kg/m^2 and a body weight of ≥50 kg (males) or ≥45 kg (females) were included. Participants were excluded if they met any of the following exclusion criteria: hypersensitivity to ciprofol or voriconazole; abnormal airway assessment; significant clinical laboratory abnormalities; the use of prescribed or nonprescribed concomitant medications within 14 days of the study; a history of respiratory, cardiovascular, renal, hepatic, gastrointestinal disease or major surgery; a history of drug or alcohol abuse or participation in any other clinical trials in the past 3 months; or smoking addiction (≥5 cigarettes daily).

Drug Administration

Twenty participants were randomly allocated to two groups to receive a single dose of 0.4 mg/kg ciprofol (treatment A) or 0.4 mg/kg ciprofol after multiple doses of voriconazole (treatment B) in either sequence AB or sequence BA during two periods.

In Group 1, participants first received a single intravenous dose of 0.4 mg/kg of ciprofol within 1 min on D1. After a one-week washout period, the participants received multiple doses of voriconazole (burden dose of 400 mg, maintenance dose of 200 mg, bid) from D8 to D13, followed by a single dose of 0.4 mg/kg ciprofol combined with 200 mg voriconazole on the morning of D14. In Group 2, participants first received multiple doses of voriconazole from D1 to D6, followed by a single dose of ciprofol combined with voriconazole in the morning of D7. After a two-week washout period, the participants received a single dose of ciprofol on D21. The doses of ciprofol and voriconazole in Group 2 were the same as those in Group 1. A schematic diagram of this study is shown in Figure 1.

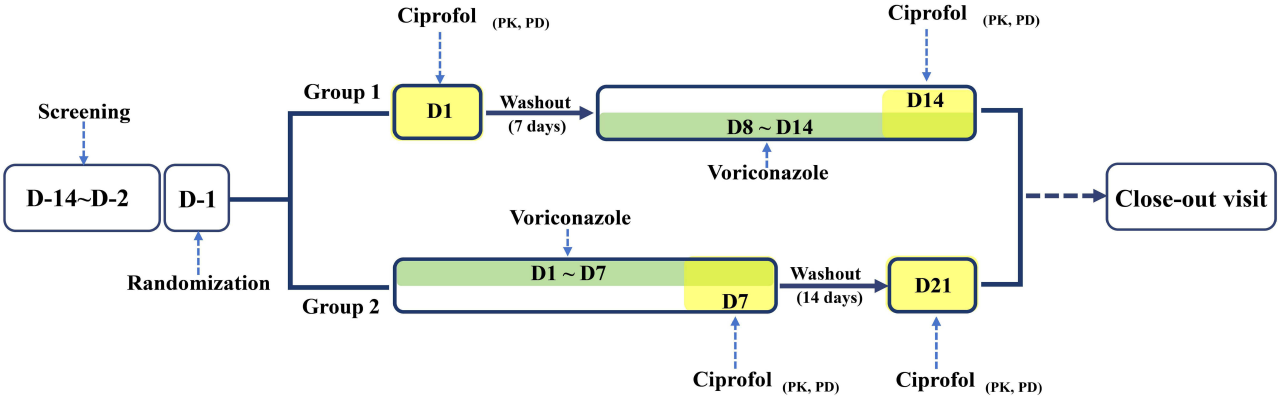

Figure 1 Schematic diagram of the two-stage crossover clinical trial to study the effects of voriconazole on ciprofol.

Sample Collection and Analysis

After each administration of ciprofol, blood samples (~3 mL) were collected from the participants at 0 h (before dosing), 1 min, 2 min, 4 min, 8 min, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, and 24 h postdose. All blood samples were centrifuged (4°C, 1700 × g, 10 min) to separate the plasma and then transferred to Shanghai Xihua Scientific Co., Ltd. (Shanghai, China) for quantitative analysis. The method of sample preparation was the same as that reported previously. Briefly, a 100 μL aliquot of plasma sample was mixed with 25 μL of 1000 ng/mL deuteration ciprofol solution (internal standard) and 275 μL of acetonitrile. The mixture was vortexed for 10 min and centrifuged at 11000 × g for 5 min. The supernatant was subjected to quantitative analysis via a validated high-performance liquid chromatography-tandem mass spectrometry (LC–MS/MS) method.[16]

Pharmacokinetics Assessment

The pharmacokinetic parameters of ciprofol were analysed by using the plasma concentration of ciprofol after each administration of the drug, either alone or in combination with voriconazole. The pharmacokinetic parameters included the maximum concentration (C_{max}), area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{0-t}), AUC from time zero to infinity ($AUC_{0-\infty}$), and elimination half-life time ($t_{1/2}$).

Pharmacodynamics and Safety Assessments

The anaesthetic effects and safety of ciprofol combined with voriconazole were carefully evaluated in this study. Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores and the bispectral index (BIS) were used to evaluate the aneathetic effect of ciprofol. MOAA/S scores were evaluated at 0 min (before dosing), every minute for the first 5 min after dosing, and every 2 min thereafter until the participants' consciousness fully recovered, which was defined as a MOAA/S score of five for three consecutive times. Moreover, the BIS was recorded at 0 min (before dosing), 1 min, 2 min, 3 min, 4 min, 6 min, 8 min, 10 min, 12 min, 15 min, 30 min, 45 min, and 60 min postdose.

Vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), manifold absolute pressure (MAP), heart rate (HR), respiratory rate (RR), saturation of peripheral oxygen (SpO_2), and 3-lead ECG, were continuously monitored throughout the entire anaesthesia period. Clinical laboratory tests (blood, serum and urine analysis), 12-lead electrocardiograms, and physical examinations were also part of the safety assessment. The adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system (version 5.0).

Statistical Analysis

Statistical analyses were performed using SAS (Version 9.4, SAS Institute Inc., USA), while non-compartment analysis (NCA) was conducted to obtain PK parameters using WinNonlin (Version 8.2, Certara Inc., USA). For sample size estimation, the following assumptions were applied: true ratio = 1.0, α = 0.05, power = 80%, intra-individual variability = 19.2%

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(conservatively overestimated based on previous PK data of ciprofol in healthy subjects). Based on these parameters, the minimum number of evaluable subjects required is estimated. Primary PK parameters, including $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, were analyzed using a mixed-effects model following logarithmic transformation. The geometric mean ratios (GMRs) of these key parameters for treatment A (ciprofol) and treatment B (ciprofol + voriconazole) and their corresponding 90% CIs were calculated. When the 90% CIs for these ratios fall entirely within the equivalence range of 80%–125%, no clinically significant drug-drug interaction (DDI) is considered to exist. The PD parameters of BIS AUC_{0-t} and BIS_{peak} were similarly analyzed using a mixed-effects model. The assessment of DDI for PD parameters followed the same criteria applied to PK parameters. Safety outcomes were presented using descriptive statistics.

Results

Subject Characteristics

A total of 20 participants enrolled in the study were randomly assigned to two groups. Two participants withdrew from the study, including one who voluntarily withdrew his informed consent before dosing and one who dropped out after voriconazole but before ciprofol administration in the first period due to an AE related to voriconazole. Finally, 19 participants who received at least one dose of the study drug were included in the full analysis set (FAS) and safety set (SS), and 18 participants who completed the study with evaluable pharmacokinetic and pharmacodynamic data were included in the PK set (PKS), PD set (PDS) and DDI evaluation set (DDIES). The demographic information of the participants is shown in Table 1. The flow diagram is presented in Figure 2.

Pharmacokinetics

The plasma concentration–time curves of ciprofol are presented in Figure 3a (linear scale) and Figure 3b (logarithmic scale). After receiving ciprofol either alone or in combination with voriconazole, the plasma exposure of ciprofol (AUC_{0-t}) were 349.87±58.82 h ng/mL and 378.77±62.21 h ng/mL, respectively, and the $t_{1/2}$ values were 3.08 ±2.07 h and 3.58±2.59 h, respectively. The detailed pharmacokinetic parameters are summarized in Table 2. The GMRs (ciprofol+voriconazole versus ciprofol alone) for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of ciprofol in plasma were 99.91%, 108.29%, and 108.79%, respectively, and the 90% confidence intervals (CIs) of the above parameters were all within the range of 80%-125%. The results of the statistical analysis of the pharmacokinetic parameters are summarized in Table 3.

Table 1 Demographic Information for the Participants

Characteristics	Total (N=19) *
Sex	
Male, N (%)	16 (84.2)
Female, N (%)	3 (15.8)
Age (year)	
Mean (Min, Max)	28.3 (19, 38)
Ethnicity	
Han Chinese, N (%)	18 (94.7)
Other, N (%)	1 (5.3)
Height (cm)	
Mean (SD)	166.4 (6.48)
Weight (kg)	
Mean (SD)	62.1 (6.17)
BMI (kg/m^2)	
Mean (SD)	22.4 (1.89)

Notes: * Nineteen participants who received at least one dose of the study drug were included in the full analysis set (FAS).

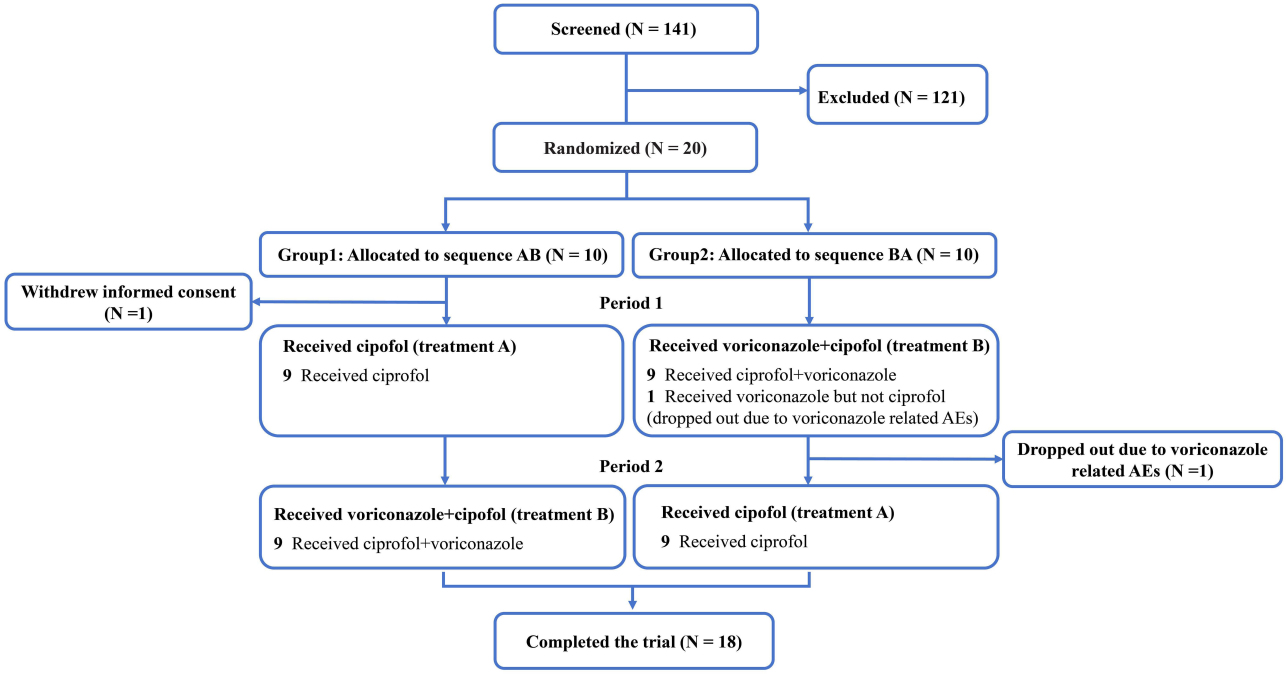

Figure 2 Flow diagram of the study participation.
Abbreviations: FAS, full analysis set; SS, safety set; PKS, pharmacokinetics set; PDS, pharmacodynamics set; DDIES, drug-drug interaction evaluation set.

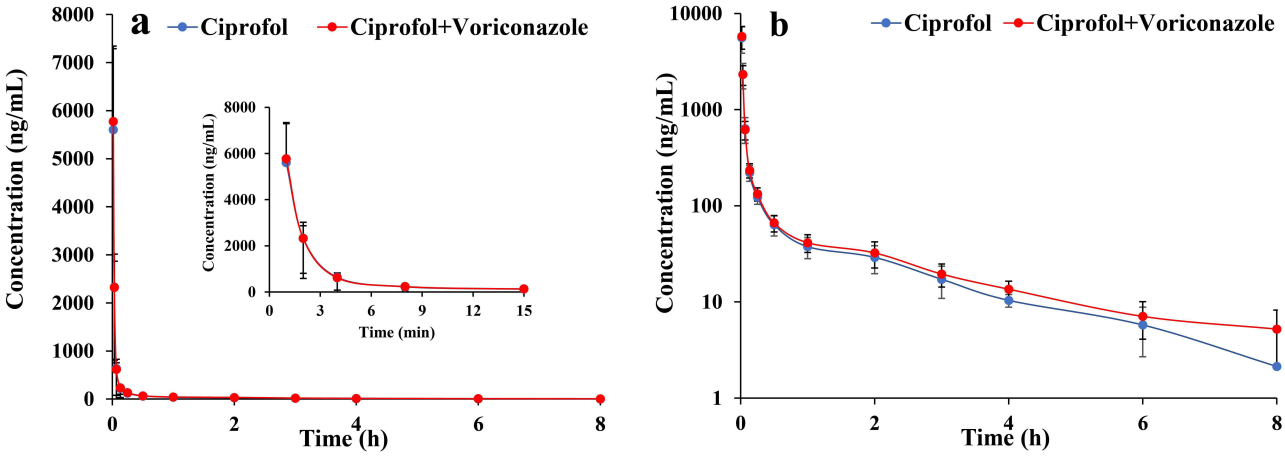

Figure 3 The plasma concentration of ciprofol after a single dose of 0.4 mg/kg ciprofol alone, or 0.4 mg/kg ciprofol following multiple doses of voriconazole. Data plot linear scale (**a**), data plot logarithmic scale (**b**).

Pharmacodynamics

The BIS value and MOAA/S score were used to estimate the pharmacodynamics of the ciprofol. The MOAA/S-time curves are shown in Figure 4a. MOAA/S score–time curves revealed that the MOAA/S scores decreased rapidly within 2 min after ciprofol administration and then recovered to baseline gradually and smoothly. The first times of MOAA/S ≤ 1 after ciprofol administration were 2.01±0.410 min (ciprofol alone) and 1.82±0.467 min (ciprofol + voriconazole). The participants regained consciousness at 11.58±3.847 min (ciprofol alone) and 11.64±3.805 min (ciprofol + voriconazole) after ciprofol administration. The detailed MOAA/S data are shown in Table 4.

The profile of the BIS–time curves (Figure 4b) was similar to that of the MOAA/S score–time curves. The mean minimum BIS value (BIS_{peak}) was 41.1 and 44.4, respectively, in participants receiving ciprofol alone or in combination

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Table 2 Primary Pharmacokinetic Parameters of Ciprofol After Receiving Ciprofol Either Alone or in Combination with Voriconazole

PK Parameter (unit)	Arithmetic Mean ± SD (%CV)	
	Ciprofol (N=18)*	Ciprofol + Voriconazole (N=18)*
C_{max} (ng/mL)	5767.22±1442.09 (25.00)	5773.89±1516.28 (26.26)
AUC_{0-t} (h ng/mL)	349.87±58.82 (16.81)	378.77±62.21 (16.42)
$AUC_{0-\infty}$ (h ng/mL)	380.00±71.97 (18.94)	412.95±74.21 (17.97)
$t_{1/2}$ (h)	3.08±2.07 (67.19)	3.58±2.59 (72.45)
λ_z (1/h)	0.30±0.13 (44.42)	0.26±0.11 (44.39)
$AUC_{\_Extrap}$ (%)	7.60±3.98 (52.3)	8.02±3.99 (49.78)
Cl (mL/h)	66757.44±11,303.77 (16.93)	60,342.69±8599.72 (14.25)
Vd (mL)	273325.60±131,137.07 (47.98)	293,244.04±168,225.04 (57.37)
$^{\#}T_{max}$ (h)	0.0167 (0.0167, 0.0333)	0.0167 (0.0167, 0.0172)

Notes: *Eighteen participants who completed the study with evaluable pharmacokinetic and pharmacodynamic data were included in the PK set (PKS). $^{\#}$ T_{max} is shown as the median (minimum, maximum).
Abbreviations: C_{max}, maximum concentration in plasma; AUC_{0-t}, area under the concentration–time curve from time zero to the last time of quantifiable concentration; $AUC_{0-\infty}$, area under the concentration–time curve from time zero to infinity; $t_{1/2}$, elimination half-life; λ_z (1/h), elimination rate constant; $AUC_{\_Extrap}$ (%), remnant area under the plasma concentration-time curve; Cl, total body clearance; Vd, volume of distribution; T_{max}, time to reach C_{max}; SD, standard deviation; %CV, percentage of coefficient of variation.

Table 3 Statistical Analysis of the PK and PD Parameters of Ciprofol After Receiving Ciprofol Either Alone or in Combination with Voriconazole

Parameter		* Geometric Mean Ratio (%)	*Ratio 90% CI (%)	Intra-individual Variation (%)
PK parameters	C_{max} (ng/mL)	99.91	92.08–108.40	14.09
	AUC_{0-t} (h ng/mL)	108.29	102.38–114.55	9.67
	$AUC_{0-\infty}$ (h ng/mL)	108.79	102.06–115.97	11.01
PD parameters	BIS_{peak}	107.05	99. 81–114.81	12.07
	BIS AUC_{0-t}	99.45	96.95–102.01	4.37

Notes: *ratio was calculated as ciprofol + voriconazole vs ciprofol.
Abbreviations: C_{max}, maximum concentration in plasma; AUC_{0-t}, area under the concentration–time curve from time zero to the last time of quantifiable concentration; $AUC_{0-\infty}$, area under the concentration–time curve from time zero to infinity; BIS_{peak}, minimum BIS value; BIS AUC_{0-t}, area under the BIS–time curve from time zero to the last time monitored; CI, confidence interval.

with voriconazole. The GMRs (treatment B versus treatment A) for the BIS_{peak} and BIS AUC_{0-t} were 108.79% and 107.05%, respectively, and the 90% confidence intervals (CIs) of the above parameters were 99.81%–114.81% and 96.95%–102.01%, respectively. The results of the statistical analysis of the BIS data are summarized in Table 3.

Safety

The vital signs of blood pressure, heart rate/pulse, respiratory frequency and blood oxygen saturation fluctuated slightly after the administration of ciprofol, but were relatively stable throughout the study and were similar between the two treatments. Compared with that at baseline, the mean arterial pressure in both treatment groups fluctuated from -18.5% to 11.7% (ciprofol alone), and from -12.6% to 12.5% (ciprofol+voriconazole). The fluctuation ranges of heart rate, respiratory rate and blood oxygen saturation after ciprofol alone were -10.2%~11.4%, -23.7%~22.3% and -1.1% ~0.1%, respectively, while those after ciprofol in combination with voriconazole were -4.5%~8.8%, -14.4%~26.4% and -0.8%~1.0%, respectively. The vital sign data are presented in Supplementary Figure S1.

Ciprofol was tolerated in participants receiving ciprofol alone or in combination with voriconazole. A total of 52 AEs related to ciprofol occurred in 31 participant-periods. The ciprofol-related AEs were all mild (grades 1–2). No serious AEs

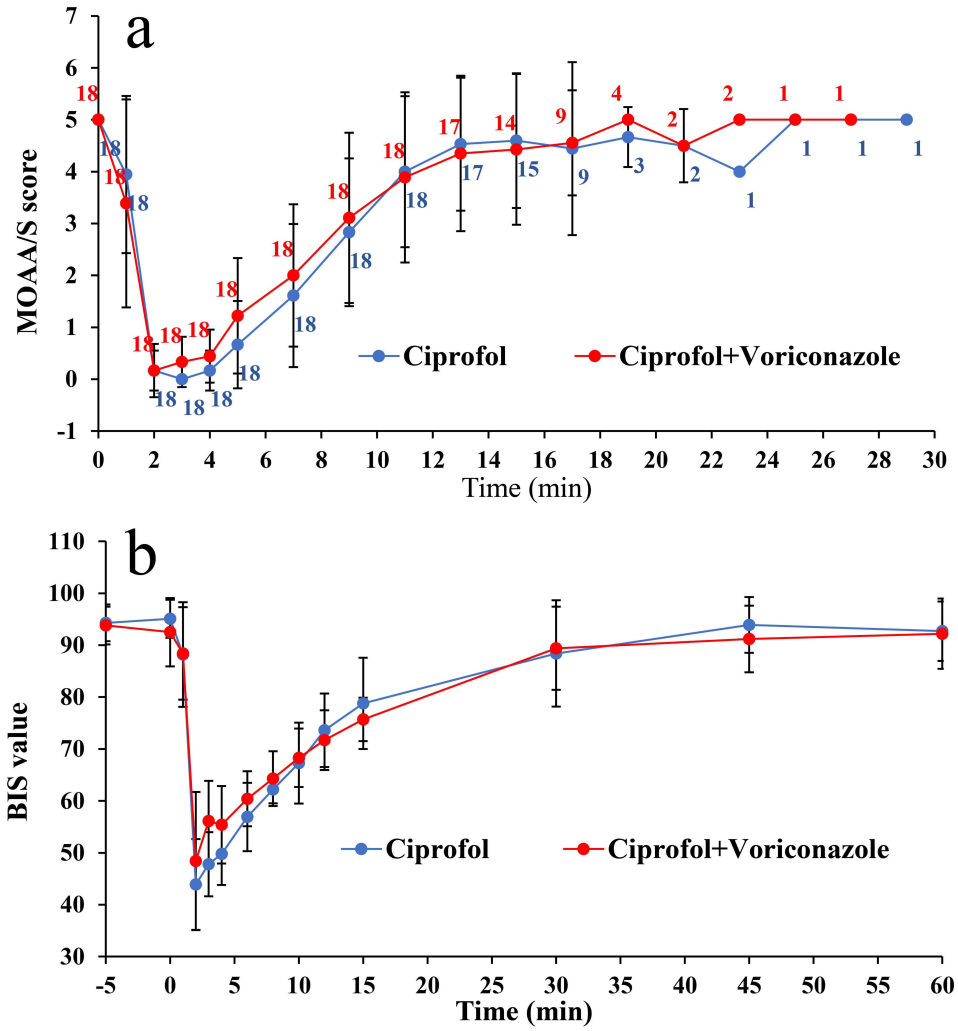

Figure 4 MOAA/S score–time (**a**) and BIS value–time (**b**) curves after ciprofol administered alone and coadministered with voriconazole. MOAA/S scores were evaluated until the participants' consciousness fully recovered. The numbers above the curves represent the number of participants included in the MOAA/S score assessment at each time point.

were observed in the study. Respiratory-related AEs were closely monitored in the study. A total of six episodes of respiratory-related AEs were reported in four participants. Specifically, during the administration of ciprofol alone, one episode of apnea, one episode of hypoxia, and two episodes of tracheal obstruction occurred. During the co-administration of ciprofol with voriconazole, two episodes of apnea were observed. Among these AEs, three episodes of apnea occurred in two participants, all of whom achieved complete recovery promptly after mask oxygen therapy. The remaining AEs resolved spontaneously without any therapeutic intervention. The summaries of the AEs are presented in Tables 5 and 6.

Table 4 Summary Table of Participants' Anaesthesia Levels After Ciprofol Administration Alone and Coadministration with Voriconazole

		Ciprofol	Ciprofol + Voriconazole
Recovery of consciousness time (min)	N (Nmiss)	18(0)	18(0)
	Mean (SD)	11.58(3.85)	11.64(3.80)
	Median	10.90	11.03
	Min, Max	6.0, 24.1	6.3, 22.1

(*Continued*)

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Table 4 (Continued).

		Ciprofol	Ciprofol + Voriconazole
Time from the start of administration to the first MOAA/S ≤1 (min)	N (Nmiss) Mean (SD) Median Min, Max	18(0) 2.01(0.41) 2.08 1.1, 3.1	18(0) 1.82(0.47) 2.07 1.0, 2.2
$MOAA/S_{min}$ = 0	N (%)	18(100)	18(100)

Abbreviation: $MOAA/S_{min}$, minimum MOAA/S score.

Table 5 Summary of Ciprofol-Related AEs That Occurred in Sequence AB and Sequence BA

	Ciprofol (N=18)		Ciprofol+Voriconazole (N=18)	
	Cases	Subjects (%)	Cases	Subjects (%)
Ciprofol-related AEs	24	15 (83.3)	28	16 (88.9)
Grade 1	22	15 (83.3)	23	16 (88.9)
Grade 2	2	1 (5.6)	5	3 (16.7)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0

Table 6 Summary of Ciprofol-Related AEs After Administration of Ciprofol Alone and Combined with Voriconazole

	Ciprofol (N=18)				Ciprofol+Voriconazole (N=18)			
	Grade 1		Grade 2		Grade 1		Grade 2	
	Cases	Subjects (%)	Cases	Subjects (%)	Cases	Subjects (%)	Cases	Subjects (%)
General disorders and site administration conditions								
Asthenia	0	0	1	1 (5.6)	1	1 (5.6)	0	0
Pain at the injection site	0	0	0	0	1	1 (5.6)	0	0
Investigations								
Gamma-glutamyltransferase increased	0	0	0	0	0	0	1	1 (5.6)
Alanine aminotransferase increased	0	0	0	0	0	0	1	1 (5.6)
Aspartate aminotransferase increased	0	0	0	0	0	0	1	1 (5.6)
Urine urobilinogen increased	0	0	0	0	1	1 (5.6)	0	0
Blood triglycerides increased	0	0	0	0	1	1 (5.6)	0	0
Blood bilirubin increased	1	1 (5.6)	0	0	0	0	0	0
Nervous system disorders								
Tic	1	1 (5.6)	0	0	3	3 (16.7)	0	0
Respiratory, thoracic, and mediastinal disorders								
Hiccough	1	1 (5.6)	0	0	0	0	0	0
Apnea	0	0	1	1(5.6)	0	0	2	2 (11.1)
Tracheal obstruction	2	2 (11.1)	0	0	0	0	0	0
Hypoxia	1	1 (5.6)	0	0	0	0	0	0
Mental illness								
Restlessness	2	2 (11.1)	0	0	4	4 (22.2)	0	0
Vascular and lymphatic disorders								
Hypotension	14	14(77.8)	0	0	12	12 (66.7)	0	0

Discussion

Ciprofol is a novel intravenous anaesthetic that has been widely used for sedation, induction and maintenance of anaesthesia in China. As a structural derivative of propofol, ciprofol has a greater affinity for $GABA_A$ receptors which makes ciprofol as effective as propofol at lower doses. The incidence of injection pain with ciprofol is also lower than that with propofol, possibly because of the lower dose of ciprofol.[4,10,20] In addition, the incidence of respiratory depression was reported to be lower in the ciprofol group than in the propofol group in a Phase III trial.[6] The many advantages of ciprofol may make it a better alternative to propofol in clinical use.

Previous studies have demonstrated that ciprofol undergoes extensive metabolism and rapid elimination in humans. CYPs and UGTs are involved in the metabolism of ciprofol, which are similar to propofol.[21] The main metabolic pathways of ciprofol include mono-oxidation, mono-hydroxylation, dihydroxylation and glucuronidation.[14] Previous clinical data and mechanistic physiologically based pharmacokinetic (PBPK) model analysis of ciprofol revealed that UGTs contribute to approximately 51.6% of ciprofol metabolism.[15] However, UGT-mediated drug glucuronidation is a Phase II metabolic reaction, the glucuronidation products of ciprofol are considered nonhypnotic and nontoxic, and the clinical effects of the glucuronidation products are negligible.[4,14]

The Phase I metabolic reaction mediated by CYPs is considered an important factor leading to clinical DDI. In accordance with the guidelines of the FDA, DDI studies should be conducted to evaluate the effects of CYP enzyme inhibitors or inducers on the pharmacokinetics and pharmacodynamics of investigational drugs to provide evidence for clinical use. The main CYPs mediating the metabolism of ciprofol were CYP2B6, CYP3A4/5 and CYP2C19, which contribute 24.2%, 7.00% (3A4), 0.68% (3A5) and 1.87% of the metabolism of ciprofol, respectively.[15]

Voriconazole is a triazole with strong potency and broad spectrum antifungal activity, and it is widely used for the management of patients infected with fungal pathogens in the clinic. Voriconazole has been shown to have a strong inhibitory effect on CYPs and is recommended as an inhibitor of CYP3A4/5, CYP2B6 and CYP2C9/19 for DDI studies of drugs metabolized by these enzymes.[18,19] Steady-state plasma concentrations are reached approximately 5 days after oral voriconazole administration, and earlier with the first loading dose of voriconazole.[22] Therefore, voriconazole was used as a perpetrator in this study to investigate the possibility of DDI in the clinical use of ciprofol.

In the pharmacokinetics study, voriconazole slightly increased the plasma exposure of ciprofol. The C_{max} and AUC_{0-t} of ciprofol were 5767.22 ng/mL and 349.87 h ng/mL, when the drug was used alone, while they were 5773.89 ng/mL and 378.77 h ng/mL when it was combined with voriconazole. The plasma half-life of ciprofol also changed from 3.08 h to 3.58 h, indicating that the elimination of ciprofol also slowed when ciprofol was combined with voriconazole. Fortunately, the 90% CIs of the GMRs for the C_{max} and AUC of plasma ciprofol were within the range of 80%-125%, which indicated that voriconazole had no significant effect on the pharmacokinetics of ciprofol. This may be attributed to the fact that ciprofol undergoes multiple enzyme-mediated metabolism in vivo, whereas voriconazole inhibits the activity of CYP3A4/5, CYP2B6, CYP2C9, and CYP2C19, but exerts minimal to negligible effects on other CYP isoforms or UGT enzymes. Thus, the metabolism of ciprofol may be compensated for by alternative metabolic pathways. Consistent with previous PBPK studies that identified UGT1A9 and CYP2B6 as the primary metabolic contributors to ciprofol metabolism, UGT1A9 may serve as the key mediator of this compensatory mechanism.[15]

Ciprofol had favourable anaesthetic properties without residual effects when it was used either alone or in combination with voriconazole. The MOAA/S scores and BIS values in the present study were in accordance with those reported in previous clinical studies.[14,23–25] Similar to the pharmacokinetic results, the combination of voriconazole had no significant effect on the efficacy of ciprofol. The 90% CIs of the GMRs for the BIS_{peak} and BIS AUC_{0-t} were within the range of 80%-125%, which indicated that voriconazole had no significant effect on the pharmacodynamics of the ciprofol. Common sedation-related AEs, including hypotension, bradycardia, apnoea, and hypoxia, were carefully monitored in this study, and there was no significant increase in the incidence and severity of AEs associated with ciprofol when ciprofol was combined with voriconazole. The above results suggest that the efficacy and safety of ciprofol are not affected even if it is used in combination with drugs that are CYP inhibitors.

Conclusions

In summary, 0.4 mg/kg ciprofol was well tolerated in combination with voriconazole, and the anaesthetic effect was satisfactory. The dose of ciprofol is suggested not to be adjusted in patients receiving the CYP inhibitor voriconazole on the basis of the PK, PD and safety characteristics.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author (Liyan Miao; E-mail: miaoliyan@suda.edu.cn; miaolysuzhou@163.com) upon reasonable request.

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Disclosure

Mengyue Hu, Yongrui Wang and Xiao Liu are full-time employees of Sichuan Haisco Pharmaceutical Co., Ltd. All the remaining authors declare no conflicts of interest for this work.

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