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Different sedation profiles with ciprofol compared to propofol represented by objective sedation level assessments by BIS and its acute hemodynamic impact in 3 escalated doses of ciprofol and propofol in healthy subjects: a single-center, open-label, randomized, 2-stage, 2-way crossover trial

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Abstract. – OBJECTIVE: To compare the sedation profiles and the pharmacokinetic, pharmacodynamic and safety characteristics of ciprofol and propofol at 3 escalated dose levels in healthy Chinese male subjects.

PATIENTS AND METHODS: Eighteen subjects were planned to be enrolled into 3 dose groups in turn: group 1 (ciprofol-0.4 mg/kg *vs.* propofol-2.0 mg/kg), group 2 (ciprofol-0.6 mg/kg *vs.* propofol-3.0 mg/kg) and group 3 (ciprofol-0.8 mg/kg *vs.* propofol-4.0 mg/kg). They were randomly assigned into a ciprofol or propofol group in a ratio of 1:1, with sequences of ciprofol-propofol or propofol-ciprofol, separated with a washout period of at least 48 h.

RESULTS: A total of 19 subjects were enrolled and 18 completed the trial. The median time to being fully alert after induction by ciprofol was longer than for propofol. The bispectral index (BIS) recovered significantly slower with ciprofol than with propofol 5 min and 10 min after reaching its lowest points. Systolic blood pressure (group 1: p=0.041; group 2: p=0.015; group 3: p=0.004) and mean arterial pressures (group 1: p=0.026; group 2: p=0.015; group 3: p=0.004) measured by the area under the curve below the baseline during the 2 min after induction were significantly less for ciprofol compared to propofol, but a significant change in diastolic blood pressure was only observed in group 3 (p=0.002). Eighteen (100.0%) subjects experienced 47 ciprofol-related treatment emergent adverse events (TEAEs) and 17 (94.4%) subjects had 54 propofol-related TEAEs, which were mainly hypotension, involuntary movements, respiratory depression, and pain at the injection site with severity of grade 1 or 2.

CONCLUSIONS: Ciprofol may be well tolerated at higher doses in the clinical practice and exhibited significantly different sedation profiles to propofol.

Key Words:
Ciprofol, Propofol, Sedation/anesthesia, Bispectral index, Hemodynamic profiles.

Introduction

Anesthetics are routinely used to relieve patients' pain during clinical diagnosis and surgical operations. Ciprofol is a novel 2,6-disubstituted phenol derivative, developed as a general

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anesthetic, that binds more effectively to gamma-aminobutyric acid-A ($GABA_A$) receptors with a comparable onset and recovery potency compared to propofol, as shown in pre-clinical studies[1]. Ciprofol administered as a single bolus intravenous (IV) injection in a Chinese phase 1 trial[2] revealed that ciprofol-induced dose-dependent sedation and general anesthesia elicited a lower degree of pain on injection and was well tolerated in the dose range 0.15-0.90 mg/kg. Several published studies[3-9] on ciprofol that investigated its actions in gastroscopy and colonoscopy procedures[3,4], fiberoptic bronchoscopy[5], general anesthesia[6-8] and ICU sedation[9] also found good tolerance and comparable efficacy compared to a 1/4-1/5 dose of propofol.

However, pain at the injection site is the most common adverse event (AE) for propofol, increasing the tension and anxiety of patients, thus directly or indirectly affecting the stability of anesthesia induction[10]. The less aqueous phase concentration of ciprofol in a 1% lipid emulsion may be the reason for the lower incidence of pain at the ciprofol injection site[11]. Additionally, the rapid and very deep sedation revealed by bispectral index (BIS), which may contribute to its actions in producing acute respiratory depression and dose-related hypotension in the elderly or sick patients, has accelerated the demand for the development of alternative drugs to propofol[12]. However, there are few studies in literature on ciprofol that have analyzed the hemodynamic profiles and blood pressure changes at specific post-induction time points instead of the continuous trend over time. Based on several previous randomized clinical trials[2,3], the present randomized crossover trial was designed for the observation of long-term blood pressure changes[14] during repeated measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) taken from the same subject. Moreover, two-stage designs were applied when the variability was unknown prior to the trial and the results of two treatments from the same individual could be obtained[13]. Thus, homogeneity and the influence of other bias factors could be effectively controlled to make the results more comparable[14,15].

Therefore, a 2-stage, crossover phase 1 trial was designed to explore whether the decrease and recovery patterns of BIS and the hemodynamic changing trends after induction of anesthesia with ciprofol and propofol were different.

Patients and Methods

Trial Design and Treatment

This was a single-center, open-label, randomized, 2-stage, crossover, phase 1 trial in healthy Chinese male subjects conducted in Sichuan Provincial People's Hospital, between May 26th, 2020, and June 22nd. The trial was approved by the Ethics Committee of Sichuan Provincial People's Hospital (approval number 2020/2-1) and written informed consent was obtained from all enrolled subjects. The trial was registered at clinicalTrials.gov (identifier NCT04294056).

The trial enrolled 18 healthy male subjects, who were randomly assigned into 1 of 3 dose groups, with 6 subjects in each group. The dose regimens were group 1 (ciprofol 0.4 mg/kg *vs.* propofol 2.0 mg/kg), group 2 (ciprofol 0.6 mg/kg *vs.* propofol 3.0 mg/kg), and group 3 (ciprofol 0.8 mg/kg *vs.* propofol 4.0 mg/kg) in two sequences. Each sequence was divided into 2 stages: ciprofol or propofol (3 level doses) was intravenously injected for 60±5 s using an injection pump after subjects had fasted for≥8 h and had been deprived of water for≥2 h; specific information on the groupings is provided in **Supplementary Table I**. Subjects in each group received a stage 1 intravenous injection and then a stage 2 intravenous injection after a washout period of≥48 h. Upon completion of the stage 2 injection, subjects were allowed to leave the trial center and were followed up by telephone 1-4 days after discharge.

Subjects

Healthy male subjects aged 18 to 45 years, weight≥50 kg, with a body mass index (BMI) range of 18 to 26 kg/m^2 were enrolled. Subjects with normal or abnormal but not clinically significant results of vital signs, physical examination, laboratory measurements, 12-lead electrocardiogram (ECG), and abdominal ultrasonography, and without obvious potential airway difficulties (with a modified Mallampati score of I or II) were also enrolled. Detailed inclusion and exclusion criteria are presented in **Supplementary File 1**.

PD Evaluations

PD evaluations included the BIS and modified observer's assessment of alert/sedation (MOAA/S) scores. BIS was recorded once at least every 1 min from the start of drug administration until the subjects were fully alert. Relevant parameters included BIS_{nadir} (BIS_{nadir} defined as the lowest BIS value), T BIS_{nadir} (the time from the start

of drug administration to the appearance of the BIS_{nadir}), BIS AUC_{0-t} (area under the time curve from time 0 to the last measured BIS value calculated by the linear trapezoid method) were also determined. MOAA/S scores were evaluated once 5 min before drug administration and then once every 1 min (±10 s) from the start of drug administration until the subjects were fully alert (i.e., the MOAA/S score was 5 for 3 consecutive measurements). The time to being fully alert was defined as the time from the start of drug administration to the first appearance of MOAA/S=5 for 3 consecutive measurements after drug administration ceased.

Pharmacokinetics (PK) Evaluations

Arterial blood samples (3±0.5 mL) were collected in EDTA-K2 anticoagulant tubes at 0, 1, 2, 4, 8, 15, 30 and 60 min, and the same volumes of venous blood samples were collected at 2, 3, 4, 6, 8, 12 and 24 h. Ciprofol and propofol plasma concentrations were measured using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS), with a low limit of quantitation (LLOQ) of 5 ng/mL. The main PK parameters included the maximum concentration (C_{max}), area under the plasma concentration-time curve (AUC_{0-t}, $AUC_{0-\infty}$), secondary PK parameters including the elimination half-life ($t_{1/2}$), time to C_{max} (T_{max}), clearance rate (CL), mean residue time (MRT), volume of distribution (V_s) and steady-state distribution volume (V_{ss}) were calculated based on a non-compartmental model using WinNonlin® (version 8.2; Pharsight Corp., Mountain View, CA, USA). The linear relationship between the main PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}) and dosage was evaluated: first, the natural logarithm conversion of PK parameters and dosage was performed; then, the model was converted to log (PK parameter)=log (α) + β log (dose) + ε. The overall slope (β) was estimated, and the 90% confidence interval (CI) of β was obtained. The relationships between the main PK parameters and time to being fully alert, BIS AUC_{0-t}, BIS_{nadir}, and T BIS_{nadir} were also analyzed for each drug dose.

Safety Evaluation

Safety evaluations included the reports of AEs, vital signs, laboratory measurements, ECG and pain on injection. All AEs were coded by systematic organ classification (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA, ver. 23.0), and the severity of an AE was graded using the Common Terminology Criteria AEs (CTCAE, ver. 5.0) guidelines[16]. All AEs were classified as treatment-emergent AEs (TEAEs), defined as any AE that occurred from the start of drug administration to the end of the follow-up period.

Vital signs, including the respiratory rate (RR), heart rate (HR), SBP, DBP, MAP, and pulse oxygen saturation (SpO_2), were measured once every 5 s from the start of drug administration until subjects were fully alert. Blood pressure was monitored invasively as the arterial blood pressure at baseline and after drug administration. The QT interval (interval from the onset of the Q-wave to the end of the T-wave), correction QT interval by Fridericia's formula (QTcF interval), PR interval (interval from the onset of P-wave to the end of the QRS complex), QRS interval (interval from the onset to the end of QRS complex) and RR interval (interval between the two QRS complex) were determined for each ECG recorded.

Statistical Analysis

Based on a previous study conducted on healthy subjects, the sample size was selected without performing a power calculation, and a total of 18 subjects (6 per group) was selected to ensure that the small sample size was adequate to assess PK, PD, and the safety characteristics in healthy subjects.

SAS software (ver. 9.4; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Continuous variables are presented as the median with range (maximum, minimum) or means ± standard deviation (SD) and categorical variables as numbers and percentages. The plasma concentration below the LLOQ was recorded as below the limit of qualification (BLQ). For the plasma concentration-time curve and calculation of PK parameters, the BLQ was calculated as 0 when appearing before T_{max}, and recorded as missing data when BLQ appeared after T_{max}. A mixed model was used to compare the time to be fully alert, and the Wilcoxon signed-rank test was used to compare the T_{max} of 2 drugs in the same group.

Results

Initially, a total of 58 subjects were screened, 19 of whom were enrolled and randomized, of which 1 subject (group 2) withdrew from the trial due to elevated blood pressure before drug administration; the remaining 18 subjects

received the drugs and completed the trial (**Supplementary Figure 1**). Finally, 18 subjects were used for the analyses of PK, PD, and safety characteristics.

As shown in **Supplementary Table II**, the demographic and baseline characteristics were consistent between the 3 groups. All subjects ranged in age from 22 to 37 years, and all had negative results of Allen's test at screening.

Ciprofol and Propofol Sedation Profiles Assessed by BIS

After injection of ciprofol and propofol, the mean BIS value rapidly decreased to the lowest value within 3 min and then gradually increased to the same level as baseline over time (Figure 1A).

Ciprofol Showed a Less Deep Level of BIS_{nadir} Compared to Propofol

In each comparison group, the mean BIS_{nadir} in the ciprofol (42.50±5.47, 36.00±3.29 and 25.67±3.01 in 0.4, 0.6 and 0.8 mg/kg) dose groups were higher than for the propofol (35.67±4.84, 24.50±3.73 and 22.83±3.60 in 2.0, 3.0 and 4.0 mg/kg) dose groups. Although significant differences were found in groups 1 and 2 (p=0.048 and p=0.002) (Figure 1B), group 3 showed a similar trend.

The median duration of BIS<30 and BIS<40 in the ciprofol groups were both shorter than for propofol in the same comparison group, in which no subject achieved a BIS<30 in the ciprofol 0.4 mg/kg, ciprofol 0.6 mg/kg or propofol 2.0 mg/kg groups, and only 1 subject achieved a BIS<40 in the ciprofol 0.4 mg/kg. The median durations of 40<BIS<60 after ciprofol administration were both longer than for propofol, with median values of 165.00 s, 422.50 s and 440.00 s, in the ciprofol 0.4, 0.6 and 0.8 mg/kg groups, respectively. The median value was 125.00 s, 202.50 s, and 185.00 in the propofol 2.0, 3.0 and 4.0 mg/kg groups, respectively (Table I).

Ciprofol Showed Slower BIS Recovery Compared to Propofol

In addition, the BIS recovery time curve within 10 min exhibited a slower increasing pattern

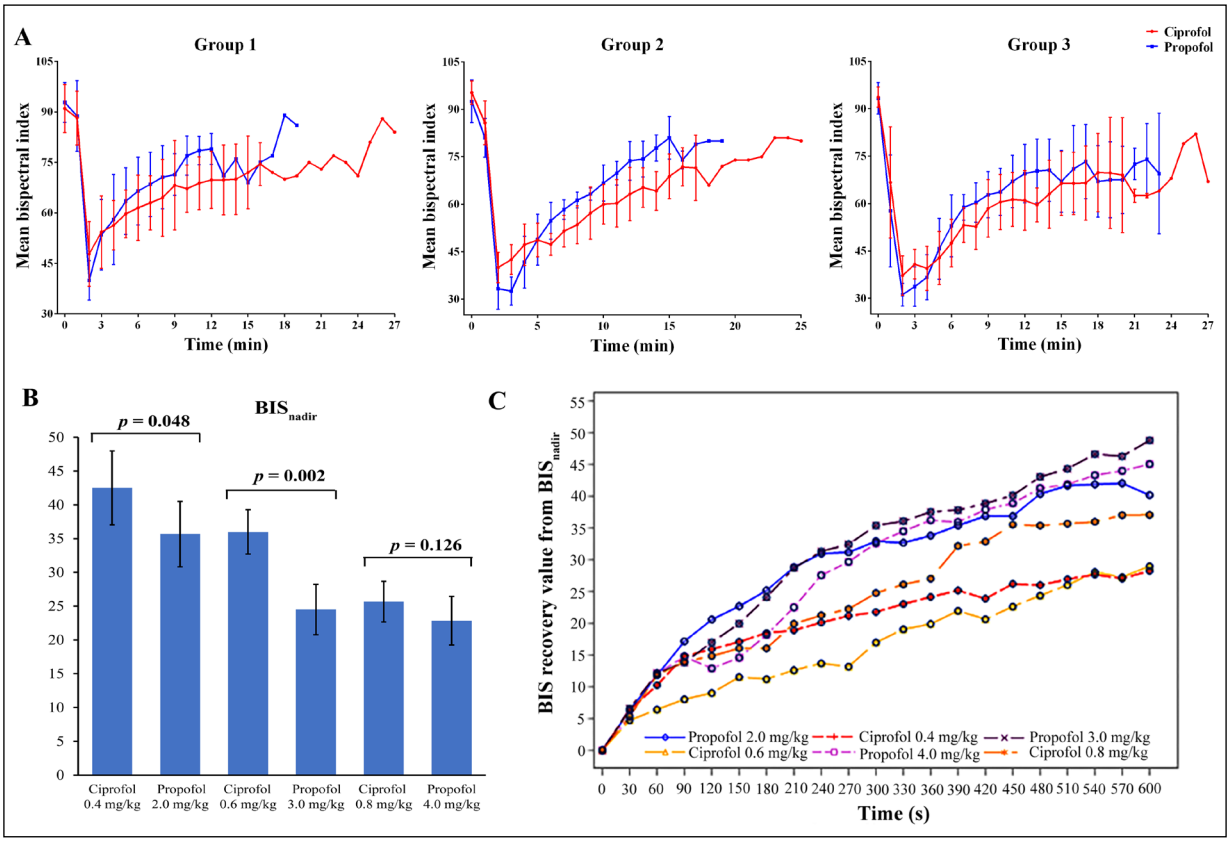

Figure 1. The dynamic change of bispectral index (BIS) assessment of alert/sedation from the start of drug administration until the subjects became fully alert in the 3 groups. **A**, from the start of drug administration until the subjects became fully alert; (**B**) BIS_{nadir}; (**C**) BIS recovery value 10 min from BIS_{nadir} (BIS presented as the mean ± SD).

Table I. Summary of times for subjects being fully alert and BIS values among the 3 groups.

	Group 1			Group 2			Group 3		
	Ciprofol 0.4 mg/kg (n = 6)	Propofol 2.0 mg/kg (n = 6)	*p*-value	Ciprofol 0.6 mg/kg (n = 6)	Propofol 3.0 mg/kg (n = 6)	*p*-value	Ciprofol 0.8 mg/kg (n = 6)	Propofol 4.0 mg/kg (n = 6)	*p*-value
Time to being fully alert (min)	11.96 (7.00, 24.98)	9.49 (5.00, 17.00)	0.002	14.99 (12.03, 23.00)	12.99 (10.98, 17.00)	0.022	16.99 (10.00, 24.97)	14.00 (10.95, 21.00)	0.278
BIS AUC_{0-t}	922.92 (692.21, 1,837.50)	752.25 (540.54, 1301.79)	-	1,006.34 (809.29, 1,572.00)	926.65 (731.33, 1,211.00)	-	1107.07 (694.50, 1,546.46)	986.48 (806.92, 1,404.67)	-
BIS_{nadir}	41.50 (35.0, 51.0)	34.50 (32.0, 45.0)	0.048	35.50 (32.0, 42.0)	23.50 (21.0, 30.0)	0.002	25.50 (22.0, 30.0)	21.50 (19.0, 29.0)	0.126
T BIS_{nadir} (min)	2.25 (1.92, 3.00)	1.83 (1.42, 1.92)	-	2.75 (1.75, 3.42)	1.63 (1.42, 4.00)	-	1.63 (1.33, 4.67)	1.46 (1.25, 2.75)	-
The duration of BIS < 30 (s)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	-	0.0 (0.0, 0.0)	37.50 (0.0, 55.0)	0.063	22.50 (0.0, 65.0)	57.50 (5.0, 125.0)	0.094
The duration of BIS < 40 (s)	0.00 (0.0, 30.0)	32.50 (0.0, 65.0)	0.063	52.50 (0.0, 90.0)	150.00 (65.0, 190.0)	0.031	137.50 (35.0, 255.0)	202.500 (55.0, 250.0)	0.156
The duration of 40 < BIS < 60 (s)	165.00 (60.0, 580.0)	125.00 (25.0, 310.0)	0.063	422.50 (315.0, 695.0)	202.50 (70.0, 295.0)	0.031	440.00 (125.0, 895.0)	185.00 (65.0, 790.0)	0.031
BIS recovery value after 5 min from lowest BIS mean (SD)	22.00 (5.90)	33.00 (8.99)	0.013	18.50 (5.96)	36.5 (3.73)	0.002	24.50 (5.32)	34.33 (9.22)	0.035
BIS recovery value after 10 min from lowest BIS mean (SD)	31.67 (10.01)	44.83 (3.76)	0.009	28.17 (7.41)	49.50 (4.04)	0.002	36.83 (9.13)	45.17 (11.65)	0.264

Data are presented as medians with ranges (min, max). The time to being fully alert was defined as the time from the start of drug administration to the first appearance of MOAA/S = 5 for 3 consecutive measurements after drug administration; BIS_{nadir} defined as the lowest BIS value; T BIS_{nadir} defined as the time from the start of drug administration to the appearance of the BIS_{nadir}; BIS AUC_{0-t} defined as the area under the time curve (AUC) from time 0 to the last measured BIS value calculated by the linear trapezoid method.

from the BIS lowest point after ciprofol induction compared to the propofol groups in all 3 different dose pairs (Figure 1C). At 5 min post lowest BIS value, the median BIS increased with a value of 22.00, 18.50, and 24.50 in the ciprofol 0.4, 0.6 and 0.8 mg/kg groups compared to 33.00, 36.50, and 34.33 in the propofol 2.0, 3.0 and 4.0 mg/kg groups (p=0.013, p=0.002 and p=0.035, respectively). At 10 min post lowest BIS value, BIS increased with a value of 31.67, 28.17 and 36.83 in the ciprofol 0.4, 0.6, and 0.8 mg/kg groups compared to 44.83, 49.50, and 45.17 in the propofol 2.0, 3.0 and 4.0 mg/kg (group 1: p=0.009; group 2: p=0.002) (Table I).

Difference of MOAA/S After Ciprofol or Propofol Administration

The median MOAA/S score-time curves of ciprofol and propofol in the 3 groups are shown in Figure 2. The MOAA/S scores for ciprofol and propofol both decreased rapidly to the minimum value, and then increased gradually with time until the MOAA/S score recovered to 5. The median time to being fully alert after ciprofol (11.96, 14.99 and 16.99 min) and propofol (9.49, 12.99 and 14.00 min) administrations both increased with increasing dosage in the 3 groups. The median time to being fully alert in subjects given ciprofol was longer than for propofol in the same group (Table I).

Plasma Concentration-Time Curve and Acute Hemodynamic Changes (SBP, DBP, MAP) After Ciprofol and Propofol Administration

The plasma concentration-time curves of ciprofol and propofol in the 3 groups are shown in Figure 3. Based on the changes in BIS profiles (decrease and recovery), we observed acute hemodynamic decreases, including in SBP, DBP and MAP between ciprofol and propofol in the same comparison group (**Supplementary Figure 2**). However, the $AUC_{0.5\text{-}2\ min}$ values of SBP (group 1: p=0.041; group 2: p=0.015; group 3: p=0.004) and MAP (group 1: p=0.026; group 2: p=0.015; group 3: p=0.004) were significantly lower for ciprofol compared to propofol in the 3 groups, while the significance for DBP was only observed in group 3 (p=0.002) (Table II).

The changes of $AUC_{0\text{-}5\ min}$ values of SBP, DBP and MAP induced by propofol induction were dose-dependent (Table II). Therefore, at high doses

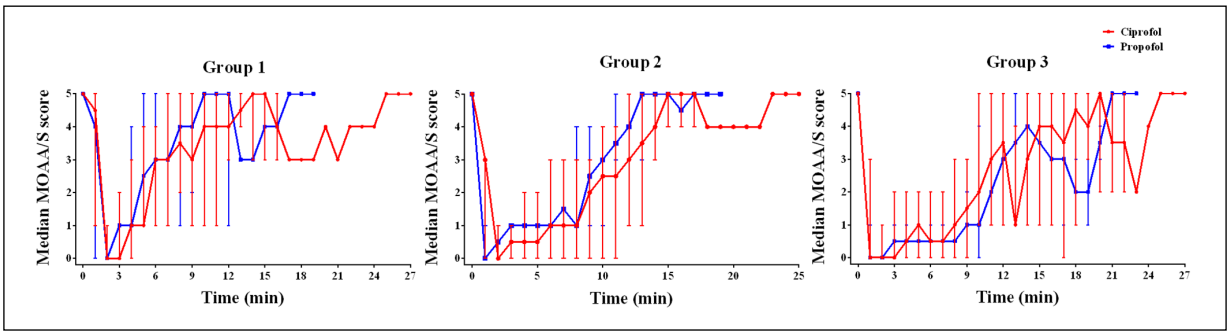

Figure 2. The dynamic change of MOAA/S from the start of drug administration until the subjects became fully alert in the 3 groups. MOAA/S score, presented as the median and range (min, max).

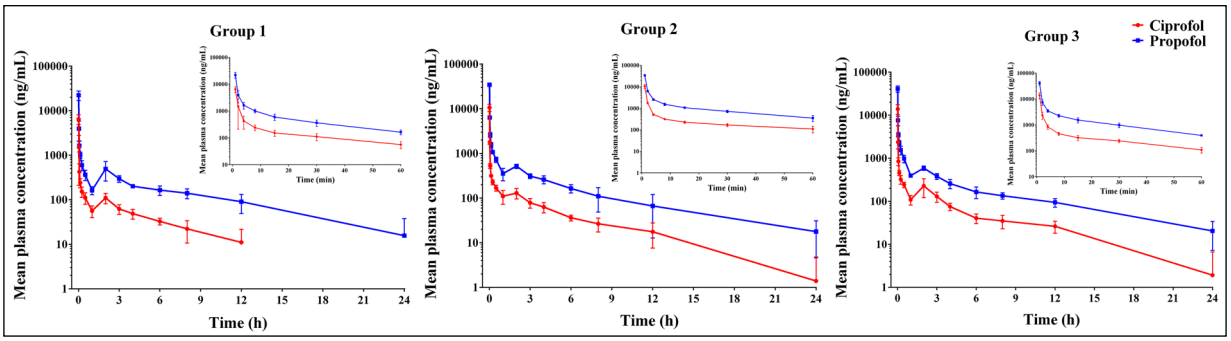

Figure 3. Mean plasma concentration-time curve (semi-log) of ciprofol and propofol in the 3 groups.

Table II. Median AUC blood pressure curve within 0 to 5 min after study drugs administration.

	Group 1			Group 2			Group 3		
AUC, Median (Min, Max)	Ciprofol 0.4 mg/kg (n = 6)	Propofol 2.0 mg/kg (n = 6)	*p*-value	Ciprofol 0.6 mg/kg (n = 6)	Propofol 3.0 mg/kg (n = 6)	*p*-value	Ciprofol 0.8 mg/kg (n = 6)	Propofol 4.0 mg/kg (n = 6)	*p*-value
$AUC_{0.5\text{-}2.0\ min}$									
AUC_{SBP} (mmHg × min)	10.96 (1.0, 18.5)	20.44 (9.7, 33.5)	0.041	18.52 (11.8, 25.3)	30.29 (18.5, 48.2)	0.015	15.33 (6.3, 26.9)	39.90 (22.0, 58.1)	0.004
AUC_{DBP}) (mmHg × min	4.50 (1.3, 8.8)	10.69 (4.4, 18.9)	0.082	9.17 (6.1, 15.5)	16.63 (10.9, 22.1)	0.065	7.46 (3.5, 13.2)	20.52 (13.8, 27.7)	0.002
AUCMAP (mmHg × min)	6.25 (0.0, 12.0)	13.67 (5.8, 23.4)	0.026	12.50 (8.5, 16.8)	21.54 (13.3, 29.2)	0.015	8.85 (5.5, 17.3)	26.56 (16.7, 35.3)	0.004
$AUC_{0\text{-}5\ min}$									
AUC_{SBP} (mmHg × min)	76.33 (55.6, 99.4)	93.35 (42.4, 157.6)	0.310	110.17 (67.5, 138.9)	138.92 (116.5, 183.4)	0.026	108.85 (60.8, 142.0)	157.13 (89.1, 205.4)	0.065
AUC_{DBP} (mmHg × min)	33.06 (20.7, 44.9)	48.81 (21.3, 77.0)	0.240	50.33 (27.0, 71.6)	57.85 (54.0, 74.9)	0.093	33.00 (29.8, 65.5)	62.06 (47.3, 79.1)	0.041
AUC_{MAP} (mmHg × min)	46.65 (34.7, 60.4)	62.38 (26.8, 102.4)	0.240	71.27 (41.8, 95.5)	91.13 (75.2, 98.6)	0.039	57.21 (39.8, 83.2)	98.00 (58.5, 111.6)	0.041

(group 3), there was a significant difference in $AUC_{0\text{-}5\ min}$ of DBP (p=0.041) and MAP (p=0.041) between ciprofol and propofol. Whether the greater change in the decrease in AUC values is related to hypotension TEAEs in the propofol groups remains to be established.

Pharmacokinetics

The drug exposure (C_{max}, AUC) of ciprofol and propofol increased with increasing dosage, both having the same median T_{max} of 0.02 h (**Supplementary Table III**). With increasing C_{max}, AUC and BIS_{nadir} exhibited downward trends, and the time to being fully alert increased slightly. The higher the plasma concentration, the lower the MOAA/S and BIS values and the lowest MOAA/S and BIS values were basically reached at C_{max}.

Safety

A total of 159 AEs occurred in the 18 subjects, all of which were TEAEs, with grade 1 (mild) for 150 TEAEs and grade 2 (moderate) for 9 TEAEs; and no TEAEs≥grade 3 nor any serious TEAEs occurred. Notably, no subjects withdrew from the trial due to the occurrence of TEAEs. The drug-related TEAEs for ciprofol and propofol were mainly hypotension, involuntary movements, respiratory depression, apnea, blood oxygen desaturation and bradycardia (Table III). Among subjects in the ciprofol group, only 1 in the ciprofol 0.4 mg/kg group experienced pain at the injection site (severity grade 1). However, 3, 2 and 1 subjects experienced pain at the injection site in the propofol 2.0, 3.0, and 4.0 mg/kg groups, respectively, with severities of grade 1, and grades 1 and 2, respectively.

Discussion

The present crossover trial was designed to make a comparison of various parameters of PK, PD and safety as well as sedation profiles for ciprofol and propofol at 3 escalated dose levels. The results revealed that ciprofol produced a longer time for a subject to become fully alert and a deeper BIS_{nadir} in the same comparison group. Note that ciprofol and propofol inductions were measured in the same subject with cross over design, which has less inherent subject variability.

Ciprofol exhibited good tolerance, a lower incidence of pain on injection and a smaller effect on blood pressure, and heart and respiration rates. The previous published two phase 3 studies[3,6] on ciprofol dosage for gastrointestinal endoscopy procedures[3] and general anesthesia induction6, allowed us to select ciprofol 0.4 mg/kg and propofol 2.0 mg/kg as the single intravenous injection dose or initial dose. Based on a previous phase 1 study[2], ciprofol was tolerated at a maximum dose of 0.9 mg/kg, thus, a maximum dose of ciprofol 0.8 mg/kg was selected. As ciprofol was 4 to 5 times more potent than propofol, the maximum dose of propofol was set at 4.0 mg/kg in the present trial.

The median time for subjects being fully alert after the administration of ciprofol was

Table III. Summary of drug related TEAEs that occurred in subjects administered ciprofol and propofol.

	Group 1		Group 2		Group 3	
Drug-related TEAEs, termed by PT, n (%)	Ciprofol 0.4 mg/kg (n = 6)	Propofol 2.0 mg/kg (n = 6)	Ciprofol 0.6 mg/kg (n = 6)	Propofol 3.0 mg/kg (n = 6)	Ciprofol 0.8 mg/kg (n = 6)	Propofol 4.0 mg/kg (n = 6)
Chills	0	1 (16.7)				
Pain at injection site	1 (16.7)	3 (50.0)	0	2 (33.3)	0	1 (16.7)
Involuntary movements	4 (66.7)	2 (33.3)	5 (83.3)	3 (50.0)	4 (66.7)	4 (66.7)
Hypotension	5 (83.3)	4 (66.7)	6 (100.0)	6 (100.0)	5 (83.3)	6 (100.0)
Respiratory depression	0	1 (16.7)	3 (50.0)	4 (66.7)	3 (50.0)	3 (50.0)
Apnea	0	0	2 (33.3)	5 (83.3)	2 (33.3)	4 (66.7)
Blood oxygen desaturation	0	0	1 (16.7)	0	2 (33.3)	2 (33.3)
Sinus bradycardia	0	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)
Bradycardia	1 (16.7)	0	0	0	0	0
Urticaria	0	0	0	0	0	1 (16.7)
Allergic dermatitis	0	0	0	0	1 (16.7)	0

TEAEs, treatment emergent adverse events; PT, preferred terms.

longer than for propofol in the same comparison groups and all times exhibited an increased trend with increasing ciprofol/propofol doses in the 3 groups. The opposite trend was observed for the BIS_{nadir}, in that with increasing ciprofol/propofol doses, the BIS_{nadir} decreased and ciprofol induced a higher BIS_{nadir} in the same comparison group. BIS can be used to guide the depth of anesthesia or sedation and reduce the risk of intraoperative awareness in surgical patients at high risk of awareness1[17-19]. In the present trial, no subjects in the ciprofol 0.4 mg/kg, ciprofol 0.6 mg/kg, or propofol 2.0 mg/kg groups achieved a BIS score<30 after induction. Even though BIS<30 occurred in 5 subjects in the ciprofol 0.8 mg/kg and BIS<40 occurred in 1, 5, and 6 subjects in the ciprofol 0.4, 0.6, and 0.8 mg/kg groups, respectively, the duration of BIS<30 and BIS<40 were obviously shorter than for propofol. Therefore, these results suggest that ciprofol has a potential neuroprotective effect. Regardless of different doses of ciprofol, the duration of 40<BIS<60 was longer than for propofol, indicating that ciprofol has superior sedation effects.

Ciprofol showed to have more stable hemodynamic characteristics, manifested by the higher values of $AUC_{0\text{-}5\ min}$ for SBP, DBP and MAP, compared to propofol in this trial. We addressed the following questions: 1) is ciprofol superior to propofol in relation to hemodynamic stability corresponding to the escalating dosage during induction due to its unique sedation profile? 2) Was there a significant difference in acute hemodynamic impact between these two drugs in the first 0-5 min after administration? In the present trial, propofol produced a larger reduction in blood pressure (SBP, DBP, and MAP) measured by the area under baseline after induction compared to ciprofol, which was the likely reason why propofol elicits more hypotension AEs at a high dose compared to ciprofol. In clinical practice, the administration of propofol is given at a fast rate. Therefore, the results of higher doses may reflect closer to real clinical practice.

Hypotension and involuntary movements were the most commonly reported TEAEs of ciprofol and propofol in this trial and also after methohexital and etomidate administration[20-23]. The higher the propofol dose, the higher the incidence of pain at the injection site[11]. However, the small sample size was a limitation of the trial, which needs further larger cohort studies to confirm the findings.

Conclusions

Compared to propofol (2.0, 3.0, and 4.0 mg/kg), ciprofol (0.4, 0.6, and 0.8 mg/kg) produced longer times for subjects to become fully alert, a higher BIS_{nadir}, and similar PK characteristics. Ciprofol was well tolerated, produced a lower incidence of pain at the injection site, and had fewer effects on BP, HR, and the RR, suggesting that it may also be useful in clinical practice when high doses are required.

Trial Registration

Clinicaltrials.gov, NCT04294056, registered on March 3rd, 2020.

Ethics Approval

The trial was approved by the Ethics Committee of Sichuan Provincial People's Hospital (approval number 2020/2-1).

Informed Consent

Informed consent was obtained from all individual participants included in the trial.

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Conflict of Interests

The authors declare no conflicts of interest.

Availability of Data and Materials

The datasets generated during and/or analyzed during the current trial are available from the corresponding author on reasonable request.

Authors' Contributions

M.-C. Yang was responsible for the conception and design of the trial. All authors were responsible for acquisition and analysis of data; furthermore, M.-T. Li, M.-C. Yang, Z.-M. Wen and X.-K. Li were in charge of statistical analysis. J. Deng, M.-T. Li and M.-C. Yang drafted the manuscript; M.-C. Yang, Z.-M. Wen, X.-K. Li, C.-Y. Zhu, T. Wang, T. Yan, M. Tang, Y. Pu and H.-Y. Zuo revised and commented the draft. All authors read and approved the final version of the manuscript.

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