Safety and efficacy of ciprofol *vs.* propofol for sedation in intensive care unit patients with mechanical ventilation: a multi-center, open label, randomized, phase 2 trial

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Abstract

Background: Ciprofol (HSK3486; Haisco Pharmaceutical Group Co., Ltd., Chengdu, China), developed as a novel 2,6-disubstituted phenol derivative showed similar tolerability and efficacy characteristics as propofol when applicated as continuous intravenous infusion for 12 h maintenance sedation in a previous phase 1 trial. The phase 2 trial was designed to investigate the safety, efficacy, and pharmacokinetic characteristics of ciprofol for sedation of patients undergoing mechanical ventilation.

Methods: In this multicenter, open label, randomized, propofol positive-controlled, phase 2 trial, 39 Chinese intensive care unit patients receiving mechanical ventilation were enrolled and randomly assigned to a ciprofol or propofol group in a 2:1 ratio. The ciprofol infusion was started with a loading infusion of 0.1–0.2 mg/kg for 0.5–5.0 min, followed by an initial maintenance infusion rate of 0.30 $mg \cdot kg^{-1} \cdot h^{-1}$, which could be adjusted to an infusion rate of 0.06 to 0.80 $mg \cdot kg^{-1} \cdot h^{-1}$, whereas for propofol the loading infusion dose was 0.5–1.0 mg/kg for 0.5–5.0 min, followed by an initial maintenance infusion rate of 1.50 $mg \cdot kg^{-1} \cdot h^{-1}$, which could be adjusted to 0.30–4.00 $mg \cdot kg^{-1} \cdot h^{-1}$ to achieve −2 to +1 Richmond Agitation-Sedation Scale sedation within 6–24 h of drug administration.

Results: Of the 39 enrolled patients, 36 completed the trial. The median (min, max) of the average time to sedation compliance values for ciprofol and propofol were 60.0 (52.6, 60.0) min and 60.0 (55.2, 60.0) min, with median difference of 0.00 (95% confidence interval: 0.00, 0.00). In total, 29 (74.4%) patients comprising 18 (69.2%) in the ciprofol and 11 (84.6%) in the propofol group experienced 86 treatment emergent adverse events (TEAEs), the majority being of severity grade 1 or 2. Drug- and sedation-related TEAEs were hypotension (7.7% *vs.* 23.1%, $P = 0.310$) and sinus bradycardia (3.8% *vs.* 7.7%, $P = 1.000$) in the ciprofol and propofol groups, respectively. The plasma concentration-time curves for ciprofol and propofol were similar.

Conclusions: ciprofol is comparable to propofol with good tolerance and efficacy for sedation of Chinese intensive care unit patients undergoing mechanical ventilation in the present study setting.

Trial registration: ClinicalTrials.gov, NCT04147416.

Keywords: HSK3486; Ciprofol; Propofol; Sedation; Mechanical ventilation

Introduction

Analgesia and sedation are important components of intensive care unit (ICU) therapies due to the high incidence of psychological stress and pain in patients undergoing mechanical ventilation.[1,2] At present, there are few sedatives commonly used in ICU patients of which midazolam, propofol and dexmedetomidine are representative. Propofol is used as a sedative in ICUs and is characterized by a rapid onset and recovery, short action time, and dose-dependent sedation depth.[3,4] During mechanical ventilation, propofol is administered as a continuous infusion due to its short duration of action and the need for consistent levels of sedation.[5] Propofol has a

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narrow therapeutic margin, and deep levels of sedation are not recommended to be applied by non-anesthetists.[6,7] Propofol is also associated with a high occurrence of dosedependent decreases in blood pressure, respiratory depression and hypertriglyceridemia, as well as propofol-related infusion syndrome (PRIS).[8,9] As a lipophilic drug, midazolam exhibits slow metabolism in patients, which may lead to drug accumulation and a deeper depth of sedation, with the need for a further prolonged length of mechanical ventilation and hospital stay.[10,11] Compared with midazolam and propofol, dexmedetomidine has a modest analgesic effect and a potential for preventing and/ or treating delirium, and does not cause significant respiratory depression, but increases the incidence of bradycardia and hypotension.[12,13] Of note, the search for the development of alternative sedatives with more safety characteristics and adequate sedation effects, especially in elderly or sick patients, has accelerated.

Ciprofol (Haisco Pharmaceutical Group Co., Ltd., Chengdu, China), a novel 2,6-disubstituted phenol derivative developed for the induction and maintenance of anesthesia, showed an improved anesthetic profile and less injection pain compared with propofol in pre-clinical studies. ciprofol is also a γ-aminobutyric acid type A (GABA$_a$)-receptor agonist,[14] and previous pre-clinical studies revealed the effective concentration 50 (EC$_{50}$) of ciprofol and propofol values for GABA$_A$-receptor mediated current enhancements of 1.1×10^{-6} mol/L and 5.3×10^{-6} mol/L, respectively, which implied that ciprofol is a more potent sedative compared to propofol. The target patients for ciprofol are in addition to ICU patients, those with indications for adult general anesthesia, anesthesia/sedation for gastrointestinal endoscopy and fiberoptic bronchoscopy. ciprofol is formulated in a 10% oil-in-water lipid emulsion with a drug concentration of 10 mg/mL. In a phase one study, the absorption, distribution, metabolism and excretion processes were evaluated.[15] A previous phase one trial with a similar sedation depth in accordance with the ICU environment was conducted in healthy subjects in two administration modes; stage one: initial dose followed by a maintenance dose (4 h) and stage two: loading dose followed by a maintenance dose (12 h). The results revealed that even though these two administration methods both achieved the target sedation goals, the loading dose followed by the maintenance dose might be improved to meet the clinical needs of rapid sedation in ICUs.[16]

Therefore, based on previous studies, this multi-center, open label, randomized, propofol positive-controlled, phase two trial was conducted to investigate the safety, efficacy, and pharmacokinetic characteristics of ciprofol, administered as a loading dose followed by a maintenance dose, for sedation of Chinese ICU patients undergoing mechanical ventilation.

Methods

Ethics apporval

The trial was approved by the Ethical Committees of The First Affiliated Hospital, Sun Yat-sen University (Approval No. 2019-037-02) and all other participating centers,

and written informed consent was obtained from all participating patients.

Study design and procedure

This was a multicenter, open label, randomized, propofol positive-controlled, phase two trial conducted in ICU patients undergoing intubation and mechanical ventilation in six research centers in China from November 22nd, 2019 to May 31st, 2020.

The entire trial included a screening period (day −1 to day 1), drug administration period (day 1 or day 1–2), and follow-up inspections (day 2 after drug administration) [Figure 1A]. The total time of drug administration including loading and maintenance infusions for each patient was at least 6 h (±30 min) and not more than 24 h (±30 min) to achieve the target sedation depth on the Richmond Agitation-Sedation Scale (RASS) score of −2 to +1, in accordance with Chinese Society of Critical Care Medicine and Clinical Practice Guidelines for Pain, Agitation/ Sedation, Delirium, Immobility (rehabilitation/mobilization), and Sleep (disruption) (PADIS).[2] Optionally, rescue therapy for sedation other than propofol could be administered if RASS score could not be maintained at −2 to +1 for ≥30 min at the prescribed maximum maintenance dose.

Remifentanil was permitted to be used for continuous intravenous analgesia (if required), at a loading dose of 0.5 −1.0 g/kg and a maintenance infusion rate of 0.02–0.15 µg·kg^{-1}·min^{-1}, before the trial drug administration period. Propofol was also permitted to be intravenously inject at 0.25–0.50 mg/kg per time for sedation before the experimental drug administration period (if required), but the last administration of propofol must have been completed for 30 min before the experimental drug administration period. In addition, the experimental drug was not to be administered until it was confirmed that the patient's baseline sedation level had reached a RASS score of ≥−2.

During the drug administration period, remifentanil and the experimental drugs (ciprofol or propofol) were used for analgesia and sedation, respectively. Remifentanil was administered with a maintenance infusion of 0.02–0.15 µg·kg^{-1}·min^{-1}, and the dose was adjusted to achieve appropriate levels of analgesia in the case of a Critical-care Pain Observation Tool (CPOT, range: 0–8) score of ≥3.

For sedation, the ciprofol infusion was started with a loading infusion of 0.1–0.2 mg/kg for 0.5–5.0 min. Then ciprofol was infused at an initial maintenance infusion rate of 0.30 mg·kg^{-1}·h^{-1} and could be adjusted by 0.05–0.10 mg·kg^{-1}·h^{-1} based on RASS score to an infusion rate of 0.06–0.80 mg·kg^{-1}·h^{-1}. For propofol, the loading infusion dose was 0.5–1.0 mg/kg for 0.5–5.0 min, followed by an initial maintenance infusion rate of 1.50 mg·kg^{-1}·h^{-1}, which could be adjusted by 0.25–0.50 mg·kg^{-1}·h^{-1} to an infusion rate of 0.30–4.00 mg·kg^{-1}·h^{-1}.

A top-up dose refers to a needed bolus dose of ciprofol (or propofol) according to the RASS scores of patients with a
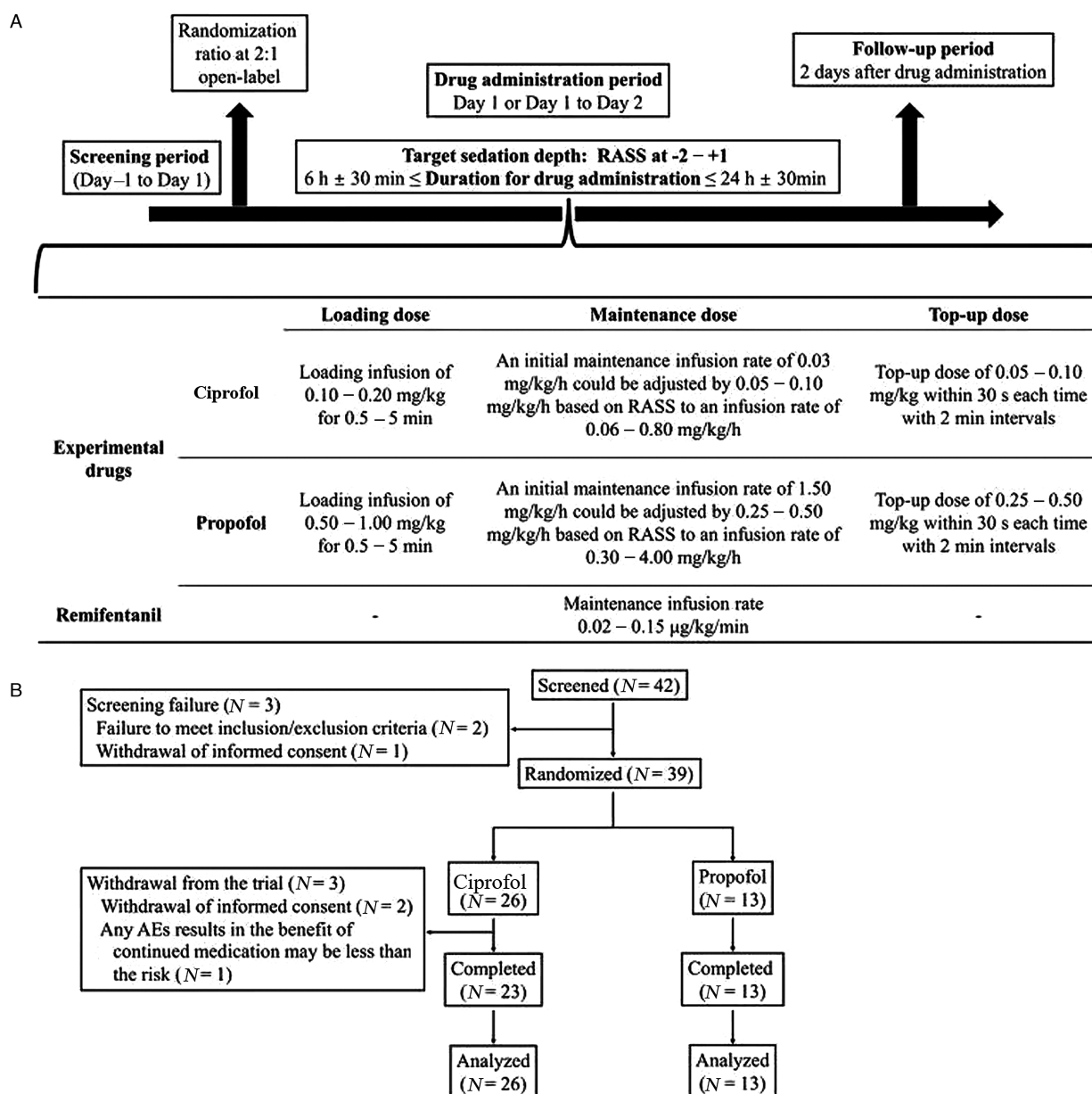
Figure 1: The (A) study procedure and (B) patient flow in the ciprofol and propofol groups.

dosage of 0.05–0.10 mg/kg (0.25–0.50 mg/kg for propofol) within 30 s each time and an interval of 2 min. In addition, if invasive or irritating procedures such as sputum aspiration occurred during the trial, an upgrade in the remifentanil dose or a top-up of the experimental drugs (ciprofol/propofol) was administered. The surgical types, durations and intra-operative anesthetic medications of the ICU patients are shown in [Supplementary Table 1, http://links.lww.com/CM9/A866].

Patients

ICU patients aged 18 to 80 years, who were expected to require sedation (RASS scores range −2 to +1) for 6–24 h due to endotracheal intubation and mechanical ventilation, were enrolled. Patients known to be allergic to egg and bean

products, opioids or their relief drugs, or propofol, or patients with contraindications to propofol, opioids and their relief drugs were excluded. Patients with a history or evidence of an increased risk during sedation/anesthesia in the screening period, including the cardiovascular system, mental disorders, cognitive dysfunction, moderate to severe hepatic and renal dysfunction, dialysis, grand mal seizure and convulsions, craniocerebral injury, intracranial hypertension, cerebral aneurysm or with an expected survival of no more than 72 h, were also excluded.

Efficacy assessments

The primary endpoint for efficacy was the average time to reach sedation compliance, defined as the average time when the hourly RASS score was in the range of −2 to +1

during the entire drug administration period. RASS score was assessed once within 30 min (±5 min) after the start of experimental drug administration for 1 h and thereafter once every 2 h (±10 min) until the end of drug administration, followed by once every 5 min (±1 min) until RASS score was ≥0. RASS also assessed when light or deep sedation occurred in subjects, or when a dose adjustment was required (especially after a loading dose, top-up dose, or prolonged sedation). The times and the related RASS score to recover to the target sedation depth were also recorded.

Secondary endpoints included the doses, titration and duration of experimental drugs, minimum maintenance dosage, remedies for sedative doses per body weight, which was defined as the average dose per body weight/h of administered sedatives other than propofol to maintain the target sedation (RASS score at −2 to +1) during the drug administration period, remifentanil dose per body weight, endotracheal extubating time and time to full alertness (details are provided in [Supplementary File 1, http://links.lww.com/CM9/A866]). An additional nursing score has been included for the evaluation of adaptive capacity for endotracheal intubation/mechanical ventilation, comprising: 1) Good (patient tolerated intubation); 2) General (patient sometimes resisted tubes); and 3) Bad (patients intolerant and required intervention to avoid self-extubating).

Safety assessments

Laboratory indicators (routine blood/urine and blood biochemistry measurements), physical examination and coagulation function was assessed at screening and during the follow-up, while an additional triglyceride test was performed within 2 h after the end of drug administration. Detailed safety measurement methods are listed in [Supplementary File 2, http://links.lww.com/CM9/A866].

All adverse events (AEs) were summarized together with treatment emergent AEs (TEAEs), using the Medical Dictionary for Regulatory Activities (MeDRA, ver. 22.1) based on systematic organ classification and preferred terms. The corresponding severity was graded using Common Terminology Criteria for Adverse Events (CTCAE, ver. 5.0). TEAE and AE definitions are presented in [Supplementary File 3, http://links.lww.com/CM9/A866].

Blood sampling and plasma drug concentration

Blood samples (3 mL) were collected within 15 min before administration of the loading dose, 4 h (±30 min) after initial maintenance dose administration, within 2 min after each adjustment and top-up dose application, and immediately (+30 s), 30 min (±3 min), 6 h (±15 min) and 24 h (±2 h) after discontinuing the maintenance medication. Blood samples were centrifuged at 1700 g (2−8°C) for 10 min and the extracted plasma stored was at −80°C for subsequent analysis. The plasma concentration was analyzed using methodologically validated liquid chromatography-tandem mass spectrometry (LC-MS/MS), with a limit of quantification (LLOQ) of 5 ng/mL. All values below the LLOQ were recorded as below the

quantitation limit (BQL), where the BQL was calculated as 0 before the first evaluable plasma concentration, otherwise the values were recorded as missing data.

Statistical analysis

The sample size was calculated based on previous clinical practice data and pharmacokinetic explorations in previous studies. Sample sizes of 30 patients (at a ratio of 2:1 for ciprofol and propofol) were required for analysis; finally, 39 patients were enrolled with an assumed dropout rate of 20% (SAS Enterprise Guide software ver. 7.1, SAS Institute, Inc., Cary, USA). A random number and a corresponding drug number for eligible patients was generated by the Central Random System, based on the interactive web response system.

All statistical analyses were performed using SAS Enterprise Guide software. Continuous variables are presented as the median (min, max) while categorical variables are presented as numbers with percentages. The Wilcoxon rank-sum test was used for comparing potential differences of continuous variables between two groups, and Fisher exact test for categorical variables. All tests were 2-sided and $P < 0.05$ was considered to be a statistically significant finding.

Demographic and baseline characteristics were analyzed based on the full analysis set (FAS), including all patients who had received the experimental drugs in accordance with the intention-to-treat principle and had a post-medication efficacy evaluation. The efficacy evaluation was also based on FAS, the missing data of RASS being filled with the last observation carried forward method. For the primary endpoint of efficacy, the linear interpolation method was used to calculate the durations of RASS score being −2 to +1 between two measured points. The Hodges–Lehmann method was used to calculate the median and 95% confidence interval (CI) of the difference in primary and secondary efficacy endpoints between the two groups. Plasma concentration was analyzed based on the pharma-cokinetic analysis set, including all enrolled patients who had received the experimental drugs with evaluable plasma concentration data. The Spearman rank correlation coefficient was used to calculate the correlation between plasma concentration and the actual ciprofol dose at each time point. The safety set (SS) included all enrolled patients who had received the experimental drug and had a post-medication safety evaluation, which was mainly used for safety analysis.

Results

Patients' disposition and baseline characteristics

A total of 42 patients were screened with 39 being finally enrolled, with 26 in the ciprofol group and 13 in the propofol group. Of the 39 patients, 36 completed the trial, while 3 patients in the ciprofol group were excluded due to withdrawal of informed consent ($n = 2$) or less benefit of continued medication $vs.$ increased risk ($n = 1$) [Figure 1B]. As shown in Table 1, the demographic and basic characteristics of patients were similar between the ciprofol and the

Table 1: Demographic and baseline characteristics of patients.

Parameters	Total (*N* = 39)	Ciprofol (*N* = 26)	Propofol (*N* = 13)	Statistic	*P* value
Age (years)	55.0 (20.0, 73.0)	54.5 (20.0, 73.0)	55.0 (28.0, 72.0)	0.746	0.456
Gender, *n* (%)				–	0.320
Male	19 (48.7)	11 (42.3)	8 (61.5)		
Female	20 (51.3)	15 (57.7)	5 (38.5)		
Height (cm)	163.0 (144, 179)	161.5 (144, 179)	167.0 (150, 175)	0.957	0.339
Weight (kg)	63.0 (42.0, 83.0)	60.5 (42.0, 81.0)	64.0 (47.0, 83.0)	0.328	0.743
BMI (kg/m^2)	22.0 (18.1, 28.9)	22.65 (19.5, 28.8)	22.50 (18.1, 28.9)	−0.268	0.788
APACHE II	9.0 (3, 18)	9.0 (3, 18)	9.0 (5, 15)	0.078	0.938
SOFA score	1 (0, 4)	1 (0, 4)	0 (0, 4)	−1.318	0.188
GCS	15 (14, 15)	15 (14, 15)	15 (15, 15)	0.974	0.330
ICU admission, *n* (%)				–	0.333
Post-operation	38 (97.4)	26 (100.0)	12 (92.3)		
Pre-operation	1 (2.6)	0	1 (7.7)		

Data are presented as the median (min, max). Wilcoxon rank-sum test was used for comparing the difference of continuous variable between two groups, and Fisher exact test was used for categorical variables comparisons. APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; GCS, Glasgow Coma Scale; ICU, intensive care unit; SOFA, Sepsis-related Organ Failure Assessment.

propofol groups (all *P* > 0.05), with a median (min, max) age of 55.0 (20.0, 73.0) years. A total of 38 patients were admitted to the ICU after surgery, while 1 patient in the propofol group was admitted to ICU due to chronic obstructive pulmonary disease before surgery.

Efficacy

Primary endpoints

The median (min, max) values of the average time to sedation compliance for ciprofol and propofol were 60.0 min (52.6, 60.0) and 60.0 min (55.2, 60.0), respectively, with a median difference of 0.00 (95% CI: 0.00, 0.00). The median (min, max) of the sedation compliance rates for the ciprofol group and propofol group were 100.0% (87.6%, 100.0%) and 100.0% (92.0%, 100.0%), respectively.

Secondary endpoints

Secondary endpoints including the total times of dose adjustments, average dose adjustments times/h, duration of loading dose, endotracheal extubating time and nursing scores were comparable between the ciprofol and propofol groups (all *P* > 0.05) [Table 2].

There were 6 (23.1%) and 5 (38.5%) cases who had at least 1 dose adjustment in the ciprofol and propofol groups, but only 2 (7.7%) in the ciprofol had received 1 top-up dose, while no patients received rescue therapy. The dosages used in ciprofol patients, such as dosage, body weight^{-1}·h^{-1}, loading dose, maintenance dose, minimum maintenance dosage (for ≥2 h and ≥4 h) were both lower than for propofol in accordance with their titer relationship of dosages (all *P* < 0.001). In addition, the total duration of drug administration (median: 10.3 *vs.* 9.2 h, *P* = 0.644), duration of maintenance dose (median: 10.3 *vs.* 9.2 h, *P* = 0.644), and remifentanil dose per body weight (2.3 *vs.* 1.6 μg/kg, *P* = 0.197) in the ciprofol group were higher than in the propofol group, while the time to

alertness (4.0 [0.0, 39.4] min *vs.* 4.5 [3.3, 24.6] min) was shorter in the ciprofol group (*P* = 0.418) (Table 2).

Safety

There were 29 (74.4%) patients who experienced 87 AEs, with 18 (69.2%) in the ciprofol group and 11 (84.6%) in the propofol group (*P* = 0.445) [Table 3].

The majority of AEs were TEAEs, with 17 (65.4%) in the ciprofol and 11 (84.6%) in the propofol group, with the most common TEAEs being hypotension (7, 17.9%), anemia (6, 15.4%), fever (6, 15.4%), elevated C-reactive protein (6, 15.4%) and hypokalemia (5, 12.8%). The reported drug related TEAEs and sedation related TEAEs were both hypotension (7.7% *vs.* 23.1%, *P* = 0.310) and sinus bradycardia (3.9% *vs.* 7.7%, *P* = 1.000) in the ciprofol and propofol groups. The severity of most TEAEs were grade 1 or 2, and only five patients experienced grade 3 TEAEs, which were hypokalemia (1, 2.6%), hypocalcemia (1, 2.6%), anemia (2, 5.1%) and hypotension (1, 2.6%). Only 1 patient with a history of hypotension (grade 2) in the ciprofol group had grade 3 hypotension associated with the drug, which was treated with a reduced dosage and infusion rate combined with noradrenaline (4 mg, i.v.) and was ameliorated. No serious AEs or deaths occurred and only one patient in the ciprofol group experienced a TEAE (epilepsy, which resulted in their withdrawal from the trial). The rate of occurrence of TEAEs associated with study procedures or concomitant medication were similar between groups. The vital signs in the ciprofol and propofol groups were relatively stable and the overall changing trend was basically similar after drug administration, in which the blood pressure and heart rate fluctuation range in the ciprofol group was smaller than in the propofol group [Supplementary Figure 1, http://links.lww.com/CM9/A866]. The mean changes in serum triglyceride concentrations from baseline to within 2 h after the end of drug administration were between 1.73 ± 1.44 and 1.31 ± 0.56 mmol/L for ciprofol and 1.09 ± 0.58 to 1.06 ± 0.46 mmol/L for propofol, which indicated that no hypertriglyceridemia occurred during sedation. The

Table 2: Summary of secondary efficacy endpoints between the two groups.

Parameters	Ciprofol (N = 26)	Propofol (N = 13)	Median (95% CI) of difference between the two groups	Statistic	P value
Usage record of experimental drugs					
Dosage per body weight per hour (mg·kg^{-1}·h^{-1})	0.30 (0.10, 0.50)	1.50 (1.10, 1.60)	−1.20 (−1.22, −1.12)	5.020	<0.001
Loading dose (mg/kg)	0.1 (0.1, 0.2)	0.5 (0.5, 0.8)	−0.40 (−0.40, −0.40)	5.491	<0.001
Maintenance dose (mg·kg^{-1}·h^{-1})	0.30 (0.30, 1.20)	1.50 (1.50, 5.00)	−1.20 (−2.20, −1.20)	5.483	<0.001
Top-up dose (mg)	0.0 (0.0, 3.1)	0.0 (0.0, 0.0)	0.00 (0.00, 0.00)	−0.974	0.330
Total times of dose adjustments	0.0 (0.0, 3.0)	0.0 (0.0, 3.0)	0.00 (−1.00, 0.00)	0.734	0.463
Average dose adjustments times per hour (times/h)	0.0 (0.0, 0.2)	0.0 (0.0, 0.4)	0.00 (−0.11, 0.00)	0.882	0.378
Number of patients who had ≥1 dose adjustment, n (%)	6 (23.1)	5 (38.5)	–	–	0.453
Total duration of drug administration (h)	10.3 (1.6, 19.4)	9.2 (6.0, 18.0)	0.90 (−2.67, 4.41)	−0.462	0.644
Duration of loading dose (min)	3.0 (0.6, 5.0)	3.1 (2.0, 5.0)	0.00 (−1.00, 0.83)	0.485	0.627
Duration of maintenance dose (h)	10.3 (1.5, 19.4)	9.2 (5.7, 17.8)	0.92 (−2.67, 4.42)	−0.462	0.644
Top-up dosing times (times)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.00 (0.00, 0.00)	−0.974	0.330
Number of patients who had ≥1 top-up dose, n (%)	2 (7.7)	0	–	–	0.544
Minimum maintenance dosage (mg·kg^{-1}·h^{-1})					
For ≥2 h	0.30 (0.20, 0.60)	1.70 (1.20, 1.80)	−1.35 (−1.37, −1.29)	5.000	<0.001
For ≥4 h	0.30 (0.10, 0.50)	1.60 (1.20, 1.70)	−1.27 (−1.29, −1.10)	4.960	<0.001
Remifentanil dose per body weight (μg/kg)	2.3 (1.2, 6.0)	1.6 (1.2, 3.1)	0.60 (−0.08, 1.04)	−1.289	0.197
Endotracheal extubating time (h)	19.4 (7.6, 36.7)	18.0 (13.7, 26.4)	0.00 (−3.72, 4.02)	0.015	0.988
Time from drug withdrawal to endotracheal extubation (h)*	1.2 (0.2, 24.0)	1.3 (0.1, 24.0)	0.00 (−1.59, 0.92)	0.000	1.000
Time to fully alertness (min)	4.0 (0.0, 29.4)	4.5 (3.3, 24.6)	−0.50 (−3.33, 0.78)	0.810	0.418
Nursing score					
Overall evaluation of adaptive capacity for endotracheal intubation/mechanical ventilation	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.00 (0.00, 0.00)	0.642	0.521

Data are presented as the median (min, max). The Wilcoxon rank sum test was used for comparing the difference of continuous variable between two groups, and Fisher exact test was used for categorical variables. In total 3 patients in the ciprofol group were not applicable due to withdrawal of informed consent (n = 2) or less benefit of continued medication vs. increased risk (n = 1).

changes in indicators related to liver and kidney function, blood routine and coagulation function before and after drug medication are shown in [Supplementary Table 2, http://links.lww.com/CM9/A866].

At baseline, there were one (3.9%) and two (15.4%) patients with positive Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) results in the ciprofol and propofol groups, but no patient developed delirium after the experimental drugs were discontinued and the CAM-ICU tests all became negative.

Plasma concentration

As shown in Figure 2, the plasma concentration-time curves for ciprofol and propofol were similar. The mean (standard deviation) plasma concentration of ciprofol reached 153.95 (60.99) ng/mL at 4 h (±30 min) after the initiation of the maintenance dose administration and reached a maximum plasma concentration of 184.51 (103.03) ng/mL at 8 h (±30 min). Subsequent plasma concentrations decreased slowly to the baseline level until 24 h (±15 min) after discontinuing the maintenance medication. The plasma concentrations for RASS values in the range of −2 to +1 were 29–185 ng/mL for ciprofol and 212–722 ng/mL for propofol. Spearman rank correlation

coefficients results revealed that the plasma concentrations in each individual patient correlated with their ciprofol dose ($r^2 = 0.6416$, $P < 0.001$) [Supplementary Table 3, http://links.lww.com/CM9/A866].

Discussion

The results of the present study revealed that the average time to sedation compliance (RAAS score −2 to +1, sedation compliance rates, total times of dose adjustments, total duration of drug administration, duration of loading dose, duration of maintenance dose, number of patients who had ≥1 top-up dose, endotracheal extubating time and nursing scores were not different in the ciprofol and propofol groups. These data indicate that ciprofol produces similar levels of sedation compared to propofol in ICU wards for patients with endotracheal intubation who are receiving mechanical ventilation to achieve required sedation times of 6 to 24 h.

During the study period, most TEAEs were grade 1 or 2 in severity and only 1 patient in the ciprofol group experienced a grade 3 hypotension that was related to the experimental drug. Generally, the category and severity of drug related TEAEs in the ciprofol group were similar to those in the propofol group. However, in the

Table 3: Summary of adverse events in the two groups.

Parameters	Ciprofol (*N* = 26)		Propofol (*N* = 13)		*P* value	Total (*N* = 39)	
	Number of AEs	Number of patients (%)	Number of AEs	Number of patients (%)		Number of AEs	Number of patients (%)
Any AEs	57	18 (69.2)	30	11 (84.6)	0.445	87	29 (74.4)
Any TEAEs	56	17 (65.4)	30	11 (84.6)	0.276	86	28 (71.8)
Drug related TEAEs	3	2 (7.7)	4	4 (30.8)	0.153	7	6 (15.4)
Sedation related TEAEs	3	2 (7.7)	4	4 (30.8)	0.153	7	6 (15.4)
Hypotension	2	2 (7.7)	3	3 (23.1)	0.310	5	5 (12.8)
Sinus bradycardia	1	1 (3.8)	1	1 (7.7)	1.000	2	2 (5.1)
Grade 3 or above TEAEs	4	4 (15.4)	1	1 (7.7)	0.648	5	5 (12.8)
Hypokalemia	1	1 (3.8)	0	0	1.000	1	1 (2.6)
Hypocalcemia	1	1 (3.8)	0	0	1.000	1	1 (2.6)
Anemia	1	1 (3.8)	1	1 (7.7)	1.000	2	2 (5.1)
Hypotension	1	1 (3.8)	0	0	1.000	1	1 (2.6)
SAEs	0	0	0	0	–	0	0
TEAEs associated with study procedure or concomitant medication	19	6 (23.1)	24	6 (46.2)	0.164	43	12 (30.8)
TEAEs leading to discontinue/withdrawal of drug administration or trials	1	1 (3.8)	0	0	1.000	1	1 (2.6)
Epilepsy	1	1 (3.8)	0	0	1.000	1	1 (2.6)

Fisher exact test was used for comparing the difference of TEAEs incidence between two groups. Hypoxemia was defined as the occurrence of SpO_2 (<90%) for >30 s; Bradycardia was defined as the occurrence of heart rate (<50 beats/min) for more than 2 min; Hypotension was defined as a SBP <90 mmHg or a 20% decline relative to baseline with a duration lasting for longer than 2 min. AEs, adverse events; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events.

present trial, the ciprofol related TEAE incidence was lower than in the propofol group, mainly because the incidence of hypotension and bradycardia was lower than in the propofol group. Whether the difference between the two groups was due to small sample sizes needs to be evaluated unequivocally in a larger trial.

Since propofol is formulated in a 10% oil-in-water lipid emulsion (10 mg/mL) it has been associated with an increased risk of development of hypertriglyceridemia and a previous study found that 27.9% of patients developed hypertriglyceridemia after cumulative propofol applications for a median time of 47 h.[17,18] In the present trial, serum triglyceride concentrations did not rise when comparing baseline with serum concentrations up to 2 h after drug discontinuation in both groups, which might be explained by the relatively short medication duration compared to 47 h in the previous study. However, it is noteworthy that the ciprofol application contains essentially less lipid since the necessary dose for sedation is about 1/5 of that of propofol. Remifentanil was permitted to be used for continuous intravenous analgesia, at a loading dose of 0.5–1.0 μg/kg (if required) and a maintenance infusion rate of 0.02 to 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$, in accordance with Clinical Practice Guidelines for PADIS.[2] In the present trial, the remifentanil dose was adjusted to achieve appropriate levels of analgesia at a CPOT score of <3, and a significant difference was not found for remifentanil dose per body weight between the ciprofol and propofol groups (*P* = 0.197).

A variety of factors have been shown to impair adrenal functions in ICU patients including the short-acting intravenous anesthetic etomidate, which suppresses adre-nocortical function by inhibition of 11 β-hydroxyl-ation.[19-21] However, compared with etomidate, immediate adrenal insufficiency occurred significantly less during propofol application for emergent endotracheal intubation in critically ill patients.[22] A limitation of the present trial was that indicators related to adrenal cortical function were not included in the outcome parameters, but ciprofol as a novel 2,6-disubstituted phenol derivative similar to propofol, may have similar effects on adrenal cortical functions, but detailed analyses of adrenal cortical functions related to ciprofol will be included in future studies.

In a previous trial, ciprofol was shown to be safe and well tolerated during colonoscopy procedure at doses ranging from 0.1 to 0.5 mg/kg.[23] Ciprofol of 0.4 to 0.5 mg/kg induced equivalent sedation/anesthesia and had a similar safety profile to propofol at 2.0 mg/kg.[24] Several unpublished studies of ciprofol, that investigated its actions in gastrointestinal endoscopy, colonoscopy and fiberoptic bronchoscopy procedures (NCT03674008, NCT04111159) and induction and maintenance for general anesthesia (NCT03698617, NCT03808844, NCT04048811, NCT04511728), also revealed good tolerance and comparable efficacy. In the present investigation, we verified the real-world applicability of ciprofol in healthy subjects from a phase 1 study by using an ICU mode of application (loading dose and mainte-nance dose).[16] Therefore, another limitation of the trial was that that there was no statistical comparison of the efficacy endpoints because the study was likely under-powered, but the efficacy data can serve for the sample size calculation in a phase 3 trial; the main focus of the present phase 2 trial was safety.
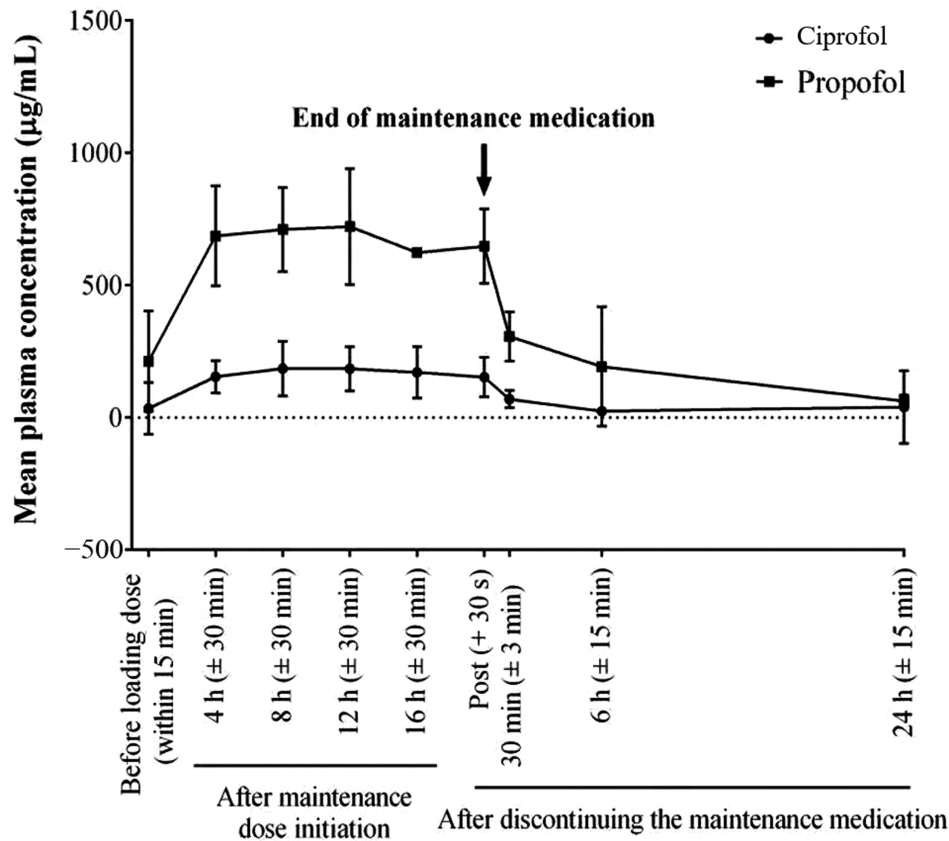
Figure 2: The plasma concentration-time curve of ciprofol and propofol. Data are expressed as the mean ± standard deviation.

In summary, the efficacy of ciprofol was comparable to propofol for light sedation of Chinese ICU patients receiving mechanical ventilation in the present study setting. The safety was comparable to propofol without significant differences in the frequency of AE occurrence ($P = 0.445$). Drug related TEAEs and sedation related TEAEs were both hypotension (7.7% *vs.* 23.1%, $P = 0.310$) and sinus bradycardia (3.8% *vs.* 7.7%, $P = 1.000$) in the ciprofol and propofol groups. Further trials of ciprofol for sedation during intensive care are warranted.

Conflicts of interest

Xiao Liu and Wei Gao are employees of Haisco Pharmaceutical Group Co., Ltd. The remaining authors declared no competing interest.

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