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ORIGINAL RESEARCH

Pharmacokinetics and Safety of Oliceridine Fumarate Injection in Chinese Patients with Chronic Non-Cancer Pain: A Phase I, Single-Ascending-Dose, Open-Label Clinical Trial

Yuncheng Ni[1,*], Ranglang Huang[2,*], Shuang Yang[3], Xiao Yan Yang[3], Shan Zeng[3], An Yao[3], Jie Huang[3], Guoping Yang[3,4]

[1]Department of Pain, The Third Xiangya Hospital and Institute of Pain Medicine, Central South University, Changsha, Hunan, 410013, People's Republic of China; [2]Department of General Surgery, The Third Xiangya Hospital, Central South University, Changsha, Hunan, 410013, People's Republic of China; [3]Center of Clinical Pharmacology, The Third Xiangya Hospital, Central South University, Changsha, Hunan, 410013, People's Republic of China; [4]Xiangya School of Pharmaceutical Sciences, Central South University, Changsha, Hunan, 410013, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jie Huang; Guoping Yang, Email cellahuang1988@163.com; ygp9880@126.com

Background: Oliceridine is a novel G protein-biased ligand μ-opioid receptor agonist. This study aimed to assess the pharmacokinetics and safety profile of single-ascending doses of oliceridine fumarate injection in Chinese patients with chronic non-cancer pain.

Methods: Conducted as a single-center, open-label trial, this study administered single doses of 0.75, 1.5, and 3.0 mg to 32 adult participants. The trial was conducted in two parts. First, we conducted a preliminary test comprising the administration of a single dose of 0.75mg to 2 participants. Then, we conducted the main trial involving intravenous administration of escalating doses of oliceridine fumarate (0.75 to 3 mg) to 30 participants. Pharmacokinetic (PK) parameters were derived using non-compartmental analysis. Additionally, the safety evaluation encompassed the monitoring of adverse events (AEs).

Results: 32 participants were included in the PK and safety analyses. Following a 2-min intravenous infusion of oliceridine fumarate injection (0.75, 1.5, or 3 mg), Cmax and Tmax ranged from 51.293 to 81.914 ng/mL and 0.034 to 0.083 h, respectively. AUC_{0-t} and half-life ($t_{1/2}$) increased more than proportionally with dosage (1.85–2.084 h). Treatment emergent adverse events (TEAEs) were found to be consistent with the commonly reported adverse effects of opioids, both post-administration and as documented in the original trials conducted in the United States. Critically, no serious adverse events were observed.

Conclusion: Oliceridine demonstrated comparable PK parameters and a consistent PK profile in the Chinese population, in line with the PK results observed in the original trials conducted in the United States. Oliceridine was safe and well tolerated in Chinese patients with chronic non-cancer pain at doses ranging from 0.75 mg to 3.0 mg.

Trial Registration: The trial is registered at chictr.org.cn (ChiCTR2100047180).

Keywords: pharmacokinetics, oliceridine, chronic pain, G-protein-biased ligand, phase I trial

Introduction

Pain management is a critical concern for both patients and physicians during the postoperative period. Inadequate treatment of postoperative pain can lead to a range of short- and long-term consequences, such as delayed recovery, psychological issues, and dissatisfaction with medical services. Patients experiencing poorly managed postoperative acute pain have an increased risk of developing chronic pain, necessitating long-term therapy and potentially experiencing adverse effects such as depression and constipation.[1]

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Conventional opioid analgesics, such as morphine, fentanyl, and hydromorphone, are typically used to treat moderate to severe post-operative acute pain.[2,3] Although effective in alleviating pain, their use is frequently limited by opioid-related adverse events (AEs) such as respiratory depression, nausea, vomiting, ileus, and excessive sedation.[4,5] These AEs can impede patient recovery in several ways, including under-dosing resulting in suboptimal analgesia, prolonged hospital stay to allow for the management of pain and emergent AEs, increased pain, and higher hospitalization costs.[6–9] Despite these drawbacks, opioids remain the cornerstone of the medical treatment of moderate to severe acute pain due to their effectiveness.[10] One approach to overcoming this limitation is the development of safer opioids that effectively treat post-surgical pain while minimizing AEs such as respiratory depression and addiction, potentially leading to faster patient recovery, shorter hospital stays, reduced medical costs, quicker return to normal activity, and enhanced patient satisfaction.[11–14]

Conventional opioids primarily bind to μ-opioid receptors, stimulating G-protein signaling and β-arrestin recruitment. Studies in β-arrestin knockout animals have shown that morphine administration results in enhanced analgesia with reduced respiratory depression and constipation compared to wild-type animals.[15–17] It is hypothesized that analgesia and adverse effects are mediated respectively by the G protein signaling pathway and the β-arrestin recruitment pathway. Selective μ-opioid receptor ligands that stimulate only G protein signaling without eliciting β-arrestin recruitment may thus offer analgesic benefits with fewer AEs.[18] However, in recent years, there has been extensive debate about the mechanisms of opioid-induced analgesia and its side effects. Kliewer et al and Kuo et al noted that ligands that favor G protein signaling, while enhancing analgesia and reducing tolerance, may also exacerbate opioid side effects. This suggests that these different effects need to be weighed when developing new opioids to ensure the safety and efficacy of the drugs.[19,20]

Oliceridine (formerly TRV130) is a novel G protein-biased ligand μ-opioid receptor agonist. Preclinical studies have demonstrated its potent analgesic effects and improved safety profile, characterized by reduced respiratory depression and gastrointestinal dysfunction compared to morphine, suggesting potential advantages in acute pain management.[11,17,21,22] Clinical studies conducted in the United States have demonstrated that oliceridine generally exhibits similar onset time, analgesic effect, duration, and predictability as morphine, while outperforming morphine in overall safety and tolerance.[23–28] Although oliceridine is a G-protein-biased μ-opioid receptor agonist that should theoretically reduce certain side effects, in the United States it still carries warning labels about addiction and fatal respiratory depression.[19] This paradox raises questions about the accuracy of existing assumptions and possible individual differences between populations or races, suggesting that further research is needed to fully understand the mechanisms of action of opioids and their safety.

In June 2020, Enhua Pharmaceutical Co., Ltd. was authorized by the NMPA to produce oliceridine, and in August of the same year, the FDA approved its marketing in the United States, marking it as the first and only G protein-biased mu-opioid receptor agonist available globally. The primary objective of this study was to assess the pharmacokinetic (PK) characteristics of oliceridine fumarate injection developed by Jiangsu Enhua Pharmaceutical Co., Ltd in Chinese participants with chronic non-cancer pain in a first-in-human clinical trial. Additionally, the tolerability and safety of this medication were also assessed.

Methods

Ethics Statement

This study was conducted at the Research Center for Clinical Trials of the Third Xiangya Hospital of Central South University. Adhering strictly to the study protocol, the research was carried out in compliance with the ethical principles of the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's Good Clinical Practice (ICH-GCP), and relevant local regulations. The Institutional Review Board of the Third Xiangya Hospital of Central South University reviewed and approved the study protocol, informed consent documents, and other relevant study forms. The study was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn; ChiCTR2100047180). All subjects provided informed consent before inclusion in this study.

Study Participants

Oliceridine fumarate injection, an opioid narcotic drug, is subject to specific regulatory considerations. According to Article 13 of the Regulations on the Administration of Narcotic Drugs and Psychotropic Drugs (Decree No.442 of the State Council), clinical trials involving narcotic and category I psychotropic drugs cannot be conducted on healthy subjects. Chronic pain, as defined by the ICD-11, is pain that persists or recurs for more than 3 to 6 months. Oliceridine fumarate injection is beneficial in alleviating such pain. In order to maintain some level of pathophysiological homogeneity in the cohort, consequently, patients with chronic non-cancer musculoskeletal pain conditions, such as scapulohumeral periarthritis, chronic low back pain, and myofascial pain syndrome were selected for this study. Inclusion criteria included: 1) Voluntary written informed consent and ability to comply with study procedures and requirements; 2) Age range from 18 to 60 years, inclusive, irrespective of gender; 3) Diagnosis of chronic musculoskeletal non-cancer pain manifested as persistent or recurring pain of 3 months or longer duration (specifically conditions such as scapulohumeral periarthritis, chronic low back pain, or myofascial pain syndrome); 4) Body mass index (BMI) between 19.0 and 30.0 kg/m^2, inclusive; 5) After a specific rest period, systolic blood pressure ranging from 90 to 140 mmHg, diastolic blood pressure from 50 to 90 mmHg, heart rate between 50 and 100 beats per minute, and oxygen saturation > 95% under indoor conditions; 6) Willingness and ability to abstain from alcohol, smoking, and prescription drugs other than the investigational drug during the study. The main exclusion criteria included: 1) Clinical history or physical examination indicating a significant medical condition (other than the study indications); 2) Abnormal vital signs or clinical laboratory findings of clinical significance; 3) Active gastrointestinal, renal, cardiovascular, hepatic, metabolic, allergic, dermatological, hematological, pulmonary, nervous system, or psychiatric diseases or disorders within 35 days prior to screening, deemed clinically significant by the investigator; 4) Use of non-steroidal anti-inflammatory drugs within one week before study commencement; 5) Clinically significant ECG abnormalities on a 12-lead ECG at screening, including QTcF ≥ 450 msec (male) or ≥ 470 msec (female); 6) Presence of peripheral vascular or rheumatologic diseases.

Study Design

This study was a single-center, open-label, dose-escalation, single-dose Phase I clinical trial, designed to investigate the pharmacokinetics and safety profile of oliceridine fumarate injection in Chinese patients with chronic musculoskeletal non-cancer pain, including conditions such as scapulohumeral periarthritis, chronic low back pain, and myofascial pain syndrome. The study comprised two parts: a preliminary trial followed by a formal trial. For safety considerations, the results of the preliminary trial were used to determine if adjustments were required for the formal trial procedure and blood sample collection timing. Initially, two individuals were pretested with a 0.75 mg dose, administered intravenously over 2 min. The formal trial was divided into three dose groups, with each group planned to include 10 participants. The doses administered were 0.75 mg, 1.5 mg, and 3.0 mg, each delivered via a 2-minute intravenous injection. The operational procedures and blood sample collection in the formal trial were consistent with those in the preliminary trial, with potential adjustments based on preliminary results.

The trial was structured into three phases: a screening period from day −28 to −2, an occupancy period on day −1 day, and an observation period from day 1 to 4. Participants completed their dosing on day 1 and were discharged from the ward on day 4, following the completion of all trial-related examinations and assessments. The trial workflow is illustrated in Figure 1. All participants were required to fast for at least 10 h prior to dosing. Blood samples were collected for pharmacokinetic analyses and safety assessments were conducted throughout the study, adhering to the established trial protocol.

PK Evaluations and Detection of CYP2D6 Genotype

PK venous blood samples were collected prior to administration on the first day, and blood draws occurred at specific intervals post-administration: 2 min, 5 min, 10 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, and 48 h. Each sample, amounting to 4mL of whole blood, was collected in EDTA-K2 anticoagulant tubes. The analysis focused solely on the concentration of oliceridine, the active ingredient of the product, as its metabolites are inactive. After collection, blood samples were centrifuged at 4°C, 2500 g, for 10 min within 60 min of collection, and then stored at −80°C until analysis.

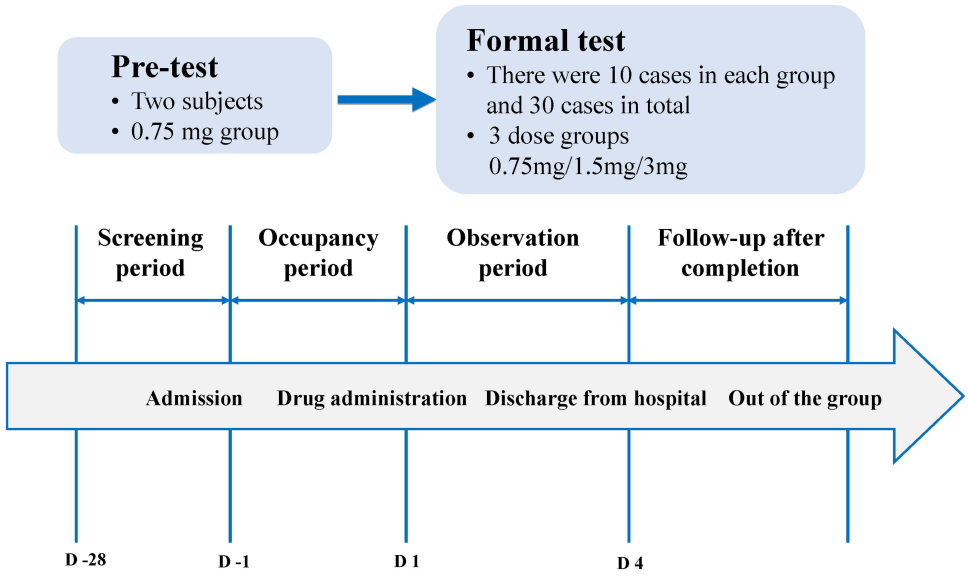

Figure 1 Study design diagram.

Plasma samples were analyzed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The analytical system comprised a Shimadzu LC-30AD liquid phase system, an API 4000 mass detector from Applied Biosystems/MDS Sciex, and an InertSustain AQ-C18 HP 3μm (2.1×100 mm) column. Deuterated oliceridine served as the internal standard, with acetonitrile as the protein precipitant. The mobile phases consisted of 100% water with 1.0% formic acid (phase A) and 100% methanol with 0.1% formic acid (phase B), at a flow rate of 0.400 mL/min. Target ions for oliceridine (m/z 387.300→m/z 127.000) and Deuterated oliceridine (m/z 390.300→m/z 130.000) were analyzed using electrospray ionization (ESI) in the multiple reaction monitoring (MRM) positive ion mode. The assay demonstrated linearity over a range of 0.0500–50.0 ng/mL, with intra- and inter-assay variability below 5%.

Non-compartmental analysis was employed to estimate various pharmacokinetic parameters. These included the peak plasma concentration (C_{max}); area under the curve extrapolated to infinity ($AUC_{0-\infty}$); area under the curve until the last measurable concentration (AUC_{0-t}); time to reach peak concentration (T_{max}); $t_{1/2}$; V_z (volume of distribution during terminal phase after intravenous administration); clearance (CL); λz (terminal rate constant), and the percentage of the AUC extrapolated from the last time point to infinity ($AUC_{\%Extrap}$). Mean residence time (MRT) was also calculated. The primary parameters for evaluating pharmacokinetic similarity were $AUC_{0-\infty}$ and C_{max}, while the others served as secondary evaluation parameters.

It was shown that oliceridine is primarily metabolized by the CYP2D6 P450 hepatic enzyme. Furthermore, oliceridine metabolism was significantly affected by CYP2D6 inhibition. In participants classified as CYP2D6 weak metabolizers (PM), oliceridine clearance was approximately 50% of that observed in extensively metabolizing (EM) individuals. This suggests a significant role for CYP2D6 in the metabolism of oliceridine. On day 2 of the study, a 5 mL venous blood sample was collected from each participant for CYP2D6 genotype testing, and then stored at −80° until analysis. The sample analysis followed the "SOP-D.GS022-ADHZ Standard Operating Procedures for Pharmacogenomics-related Gene Detection (High-Throughput Sequencing Method) (Twist Bioscience) 3.2". The process involved DNA probe capture technology: initially, 200ul of whole blood was used for DNA extraction. The extracted DNA underwent fragmentation, end-repair with A-tail addition, and ligation to construct the library. The library was then hybridized with probes, purified, mixed, denatured, and loaded into sequencing sample wells. High-throughput sequencing was performed using the NextSeq CN500 sequencer. Genotypes and metabolic phenotypes were determined through Pharmacogenomics Analysis Software V1.0 analysis, supplemented by literature.[29]

Safety Evaluations

Safety assessments were conducted through patient interviews and monitoring for AEs. Key indicators for evaluation included vital signs (blood pressure, heart rate, respiration rate, and temperature) conducted before drug administration (−1 h~0 h), then 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 24 h, 48 h, and 72 h after initiation of drug administration; physical examinations at discharge on day 4; 12-lead ECG performed at 48 h and 72 h after initiation of drug administration; Holter monitoring conducted continuously from 30 min prior to dosing until 24 h after the initiation of the dosing; laboratory tests including routine bloods, urine, blood biochemistry in the fasted condition, coagulation function tests, and others done at 72h after administration; oxygen saturation measured before administration (−1 h~0 h), then 5 min, 10 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, and 8 h after initiation of drug administration; injection site assessment in which we evaluated pain, induration, erythema, hardness/lumps at the injection site before administration (0 h), then 0.5 h, 1 h, 2 h, 4 h, and 6 h after the start of administration; and AEs. Detailed records were maintained, encompassing the clinical features, severity, onset and resolution times, duration, treatment interventions, and outcomes of AEs. The clinical significance of the AEs was assessed by the principal investigator.

Estimation of Sample Size

According to the guidance provided by the European Medicines Agency (EMA),[30,31] the number of participants in each dose group ranges from 8 to 12 cases, and we mainly conducted PK study in this trial, 10 cases in each dose group of the formal test can basically examine the PK characteristics of the participants, and the population we studied is chronic non-cancer pain patients, which is a relatively healthy population with little variability, and it can fulfill the objectives of the PK test. There were three dose groups in this clinical trial, with 2 participants in the preliminary group, and a total of 32 cases in the preliminary and formal test received the test drug and completed the trial.

Statistical Analysis

The safety analysis encompassed all participants who received the investigational drug and had recorded safety data in the safety analysis set. For the PK analysis, participants with at least one blood concentration data point and at least one effective PK parameter during the trial were included in the PK concentration set and PK parameter set, respectively. Missing data were not estimated in this study and all analyses were based on observed cases. For the safety analysis, any missing data points were assumed to be non-adverse unless otherwise indicated. In the PK analysis, missing concentration data points were not imputed, and only participants with complete and reliable data were included in the final PK concentration and PK parameter sets.

For the plasma concentration (C)-time (t) data of oliceridine, both individual and averaged c-t curves were generated. Key statistical measures at each time point, including mean concentration, standard deviation, median, maximum value, minimum value and coefficient of variation, were compiled. Pharmacokinetic parameters calculated included C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, CL_z, V_z, and $t_{1/2}$. These calculations were performed using non-compartmental models in WinNonlin software (version 6.4 or above). For each parameter, arithmetic mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean were determined. These parameters were further analyzed based on the CYP2D6 phenotype, distinguishing poor metabolizers from non-poor metabolizers. To investigate dose-exposure relationships, a power function model was used, focusing on C_{max}, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$, with linearity assessed by the inclusion of "1.0000" in the 95% confidence interval of the slope. Linear regression analysis incorporated the logarithm of the administered dose against in vivo exposure levels (AUC or C_{max}).

Safety evaluations were meticulously catalogued and summarized by study treatment group. This included the incidence and systematic categorization of AEs. The analysis encompassed adverse events, the number of cases and instances of adverse reactions categorized by system and severity, and drug-related adverse reactions, all of which were compared between groups using Fisher's exact test or chi-square tests. Additionally, other safety indicators such as oxygen saturation, vital signs, physical examination, laboratory tests, ECG, etc., were presented in a descriptive format. Furthermore, we detailed the CYP2D6 phenotypes of the participants, emphasizing any significant variations in metabolizer status.

Results

Study Participants

The study recruited the first participant on June 20, 2021 and concluded the final follow-up on September 13, 2021. Of the 145 individuals initially screened, 112 did not meet the inclusion criteria. Consequently, 33 individuals qualified for the study. One participant subsequently withdrew from the trial before drug was administered, leaving 32 participants who were administered the drug and completed the trial. The distribution was as follows: 12 participants were in the 0.75 mg dose group (2 in the pre-trial and 10 in the formal trial); 11 participants were enrolled in the 1.5 mg dose group (with 1 premature withdrawal and 10 completing the trial); and 10 participants in the 3.0 mg dose group (Figure 2).

Table 1 summarizes the demographic data and baseline characteristics of the participants by group. There were no significant differences in age, height, weight, or body mass index (BMI) across the groups. All participants were chronic non-cancer pain patients. The mean age was 31.4 ± 10.00 years, with 17 males (51.5%), predominantly of Han ethnicity (29, 87.9%). The average body weight was 64.82 ± 11.968 kg, and the mean BMI was 23.65 ± 3.086kg/m^2.

Genotypic Results

All 32 participants underwent CYP2D6 genotyping. The Results revealed 30 instances of the fast metabolism type, 2 of either fast metabolism or ultra-fast metabolism types, and no cases of intermediate or slow metabolism types.

PK Evaluations

Plasma concentrations were pooled and analyzed based on the PK concentration sets (PKCS). The mean plasma oliceridine concentration-time and semilogarithmic curves by dose group are depicted in Figure 3. For values below the lower limit of quantitation, the graph displays 0 before the T_{max} and ND after T_{max}.

In the PK evaluation of oliceridine, the individual peak plasma concentrations were analyzed for each dose group. In the 0.75 mg group, 91.7% of participants (11 of 12) achieved C_{max} approximately 2 minutes post-administration, while one participant (8.3%) reached C_{max} around 5 minutes. In the 1.5 mg group, 90% of participants (9 of 10) attained peak concentration at about 2 min, and one participant (10%) at about 3 min. For this latter individual, the administration

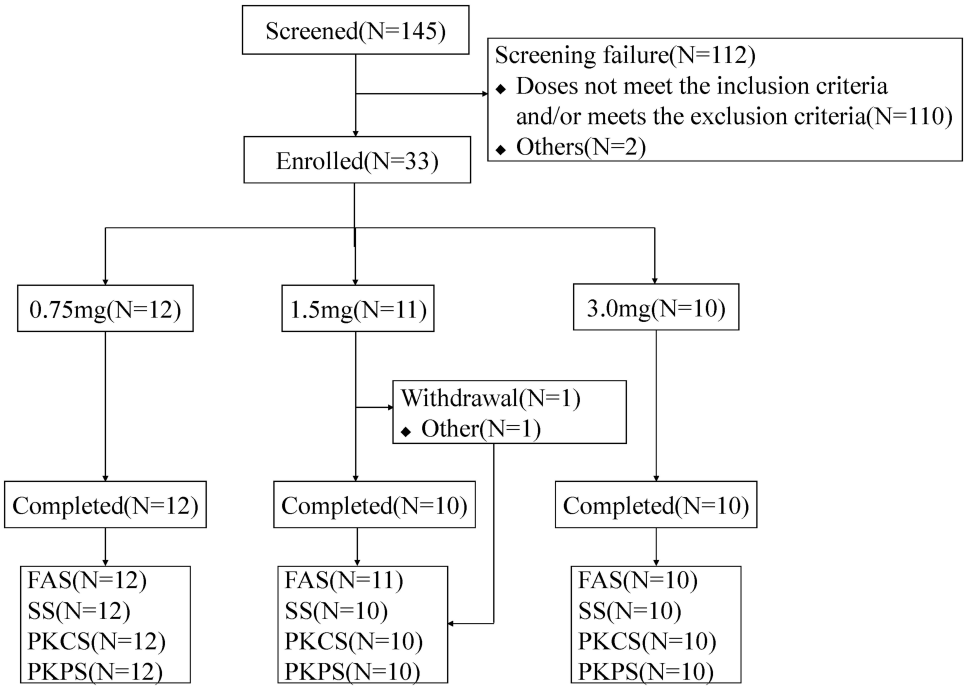

Figure 2 Flow chart of participant distribution.
Abbreviations: FAS, full analysis set; SS, safety set; PKCS, pharmacokinetics concentration set; PKPS, pharmacokinetics parameter set.

Table 1 Demographic Data and Baseline Characteristics of the Study Participants (mean±SD)

Parameter	0.75mg (N=12)	1.5mg (N=11)	3.0mg (N=10)	Total (N=33)
Age (years)				
Mean±SD	36.3±12.25	28.3±8.47	28.9±6.42	31.4±10
Min~Max	19~56	19~43	19~36	19~56
Sex				
Male, n (%)	5(41.7%)	8(72.7%)	4(40.0%)	17(51.5%)
Female, n (%)	7(58.3%)	3(27.3%)	6(60.0%)	16(48.5%)
Ethnicity				
Han Chinese n(%)	10(83.3%)	9(81.8%)	10(100.0%)	29(87.9%)
Other n(%)	2(16.7%)	2(18.2%)	0(0%)	4(12.1%)
Height(cm)				
Mean±SD	163.79±9.245	166.23±6.802	165.35±9.713	165.08±8.454
Min~Max	152.5~179.5	156.5~178.0	153.0~181.5	152.5~181.5
Weight(kg)				
Mean±SD	64.53±10.445	67.65±11.282	62.04±14.699	64.82±11.968
Min~Max	46.4~84.2	51.6~85.9	49.8~90.0	46.4~90.0
BMI(kg/m^2)				
Mean±SD	23.98±2.652	24.43±3.512	22.40±2.993	23.65±3.086
Min~Max	19.6~29.3	20.2~29.5	19.7~28.2	19.6~29.5

Abbreviation: BMI, body mass index.

duration exceeded protocol specifications due to intravenous line blockage; consequently, their C_{max} and T_{max} data were excluded from the primary PK parameter sets(PKPS) analysis, but included in a sensitivity analysis to assess result robustness. In the 3.0 mg group, 40% of participants (4 of 10) attained peak at about 2 min, 10% (1 participant) at around 10 min, and the remaining 50% (5 participant) (50%) at approximately 5 min.

Pharmacokinetic parameters for oliceridine were computed based on the PK parameter sets (PKPS). and the results for each group are summarized in Table 2. To assess the normality of the primary PK parameters: C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, in relation to the administered dose using a power function model, the logarithms of these parameters were taken. The Shapiro–Wilk test was performed using SPSS software to evaluate their normality. Based on the results of the normality test, linear regression analysis was then applied accordingly. The results, detailed in Table 3. The p-values indicate that none of the PK parameters significantly deviate from a normal distribution, as all p-values are greater than 0.05. Within the dose range of 0.75 mg to 3.0 mg, the 95% confidence interval of the slopes of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ against dose included 1, demonstrating a linear relationship between drug dose and cumulative drug exposure (AUC). However, the 95% confidence interval for the slope relating to C_{max} did not include 1, with its upper limit resting below 1 (0.7103), a finding that was consistent with the results of the sensitivity analysis. Figure 4 showed a plot of the dose-exposure relationship and a plot of the dose-exposure logarithmic relationship.

Comparison with Original Test Data

The study's PK data specifically focusing on parameters such as $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, V_z, CL, and $t_{1/2}$, were systematically compared with the reported findings from the original study conducted in the United States (CP130-1002, CP130-1003, CP130-1005A). These comparisons, detailed in Table 4 and Table 5, reveal that the C_{max} in this study was marginally higher than in the original research. However, other PK measures such as AUC, V_z, CL, and $t_{1/2}$ closely mirrored the original data.

A critical aspect of this comparison involved analyzing the blood sample collection timings, as shown in Table 6. Both in this and the original study, C_{max} predominantly occurred at the initial time point ("time 0"), followed by the "5min" and "10min" intervals. Notably, as described in Table 7, "time 0" in this study was defined as the moment immediately following infusion cessation, with an actual average blood collection time of 2.04 minutes after the infusion commenced. In contrast, the original study "time 0" was set just before the end of the infusion. In the original 1002 trial(CP130-1002), the average

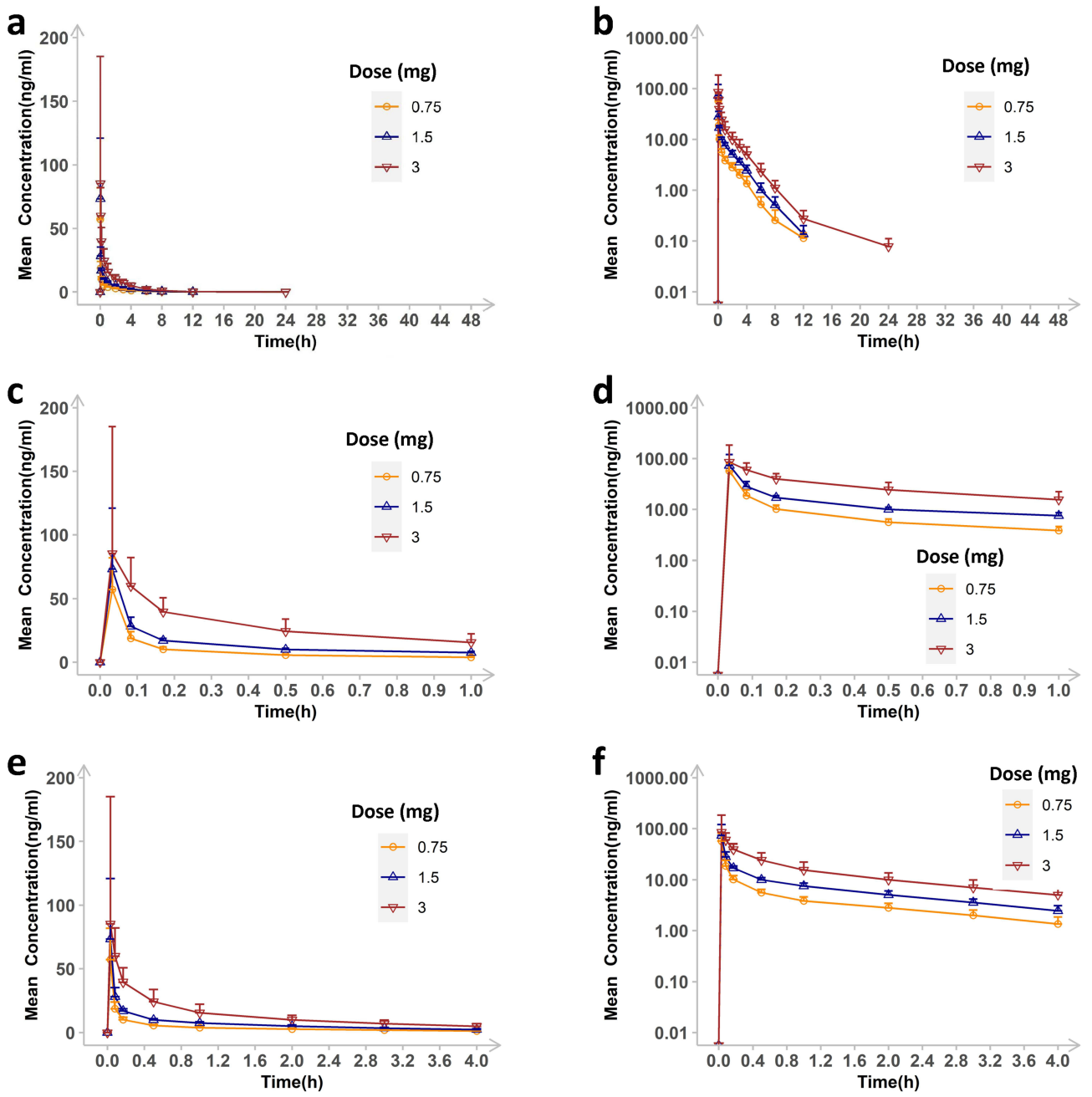

Figure 3 Mean plasma concentration–time curves. (**a**) Mean plasma concentration-time plot (Mean+SD) (**b**) Semilogarithmic scale diagram (Mean+SD) (**c**) Mean plasma concentration-time plot (0–1h) (Mean+SD) (**d**) semilog scale diagram (0–1h) (Mean+SD) (**e**) Mean plasma concentration-time plot (0–4h) (Mean+SD) (**f**) semilog scale diagram(0–4h) (Mean+SD).

collection time was 1.75 min post-infusion start, while the 1003(CP130-1003) and 1005A(CP130-1005A) trials set this time slightly earlier, at 1.5 min and within 30 seconds before infusion completion, respectively. This timing difference is significant: in the original study, the infusion was not entirely complete at "time 0", meaning a portion of the drug had not yet entered the body. Conversely, in this study, the entire drug dose was administered by "time 0". This discrepancy likely accounts for the observed slight variation in C_{max} in this study compared to the original data. Moreover, both studies exhibited high variability in C_{max}, with this study ranging from 58.47% to 71.03% and the original 1002, 1003, and 1005A trials showing variabilities of 12.27% to 39.62%, 65.7% to 70.4%, and 73.4% to 94.6%, respectively. Such significant individual variability is another potential factor contributing to the C_{max} discrepancies between this and the original studies.

Table 2 Oliceridine Pharmacokinetic Parameters (GeoMean (CV%) or Median (Min, Max))

Parameter	0.75 mg (GeoMean(CV%))	1.5 mg (GeoMean(CV%))	3.0 mg (GeoMean(CV%))
N	12	10*	10
C_{max}	51.293 (58.47)	65.969 (71.03)	81.914 (69.84)
AUC_{0-t}	19.199 (22.13)	34.249 (11.22)	69.096 (26.39)
$AUC_{0-\infty}$	19.528 (22.24)	34.668 (11.38)	69.783 (25.85)
$AUC_{-\%Extrap}$	1.620 (30.33)	1.064 (57.55)	0.748 (105.00)
T_{max}	0.034 (0.034, 0.087)	0.034 (0.033, 0.035)	0.083 (0.034, 0.168)
$t_{1/2}$	1.850 (28.01)	1.874 (14.85)	2.084 (28.80)
λ_z	0.375 (28.01)	0.370 (14.85)	0.333 (28.80)
CL	38.406 (22.24)	43.267 (11.38)	42.991 (25.85)
V_z	102.522 (23.63)	116.961 (11.85)	129.273 (40.11)
MRT	1.992 (22.60)	2.147 (19.53)	2.272 (28.07)

Notes: T_{max}(day): median (min, max); CV: coefficient of variation; *C_{max} and T_{max} values of subject TRV-B102 assigned to the 1.5 mg group were not included in the primary analysis of PKPS due to (1) blockage of the intravenous line during drug administration and (2) the resultant increased administration time required which exceeded protocol requirements. However, this subject's data were included in the sensitivity analysis for the robustness of the test results. As such, only 9 subjects were pooled for the PKPS analysis.

Abbreviations: C_{max}, peak serum concentration; AUC_{0-t}, area under the blood concentration-time curve from 0 to t time; $AUC_{0-\infty}$, area under the blood concentration curve from 0 to infinity time; $AUC_{-\%Extrap}$, percentage of residual area; T_{max}, time of occurrence of C_{max}; $t_{1/2}$, terminal phase half-life; λ_z, terminal rate constant in noncompartmental mental analysis; CL, clearance; V_z, volume of distribution during terminal phase after intravenous administration; MRT, mean dissolution time.

Table 3 Analysis of Dose-Proportionality

Parameters	N	W-Statistic*	p-value	Correlation Coefficient	Coefficient of determination R^2	Intercept	Slope	95% CI
C_{max}(ng/mL)	31	0.964907	0.3718	0.3265	0.1066	4.0396	0.3384	−0.0336, 0.7103
AUC_{0-t}(ng·h/mL)	32	0.964891	0.3715	0.9356	0.8753	3.2023	0.9212	0.7916, 1.0509
$AUC_{0-\infty}$(ng·h/mL)	32	0.97989	0.8096	0.9356	0.8753	3.2175	0.9161	0.7872, 1.0450

Note: *W-Statistic: The test statistic for the Shapiro–Wilk test, which assesses the normality of the data.

Abbreviations: ng, nanogram; mL, milliliter; h, hour; CI, confidence interval.

Safety Evaluations

No SAEs were reported among the participants, and none of the TEAEs led to discontinuation of the study.

Among the 32 participants who received the investigational product and completed the study, the incidence of TEAEs was 84.4% (27/32). This included an 84.% (27/32) incidence of mild TEAEs and a 3.1% (1/32) incidence of moderate TEAEs. There were no reports of severe TEAEs, nor were there any serious adverse events or AEs that resulted in study discontinuation. Notably, the frequency of TEAEs observed in participants increased with the administered dose. An overview of TEAEs observed in this study is detailed in Table 8.

In total, 80 adverse reactions were recorded across 26 patients, resulting in an incidence rate of 81.3% (26/32), all of which were classified as mild. The nature of TEAEs reported in this study aligns with the common adverse reactions typically associated with opioid administration and were consistent with those observed in the original study.

Discussion

Oliceridine, a G-protein-biased ligand, preferentially stimulates G-protein signaling over β-arrestin recruitment.[11,17,21,22] Previous analytical and animal research has demonstrated that this biased signaling profile effectively produces significant analgesia while significantly reducing μ-opioid receptor-mediated adverse effects, such as respiratory

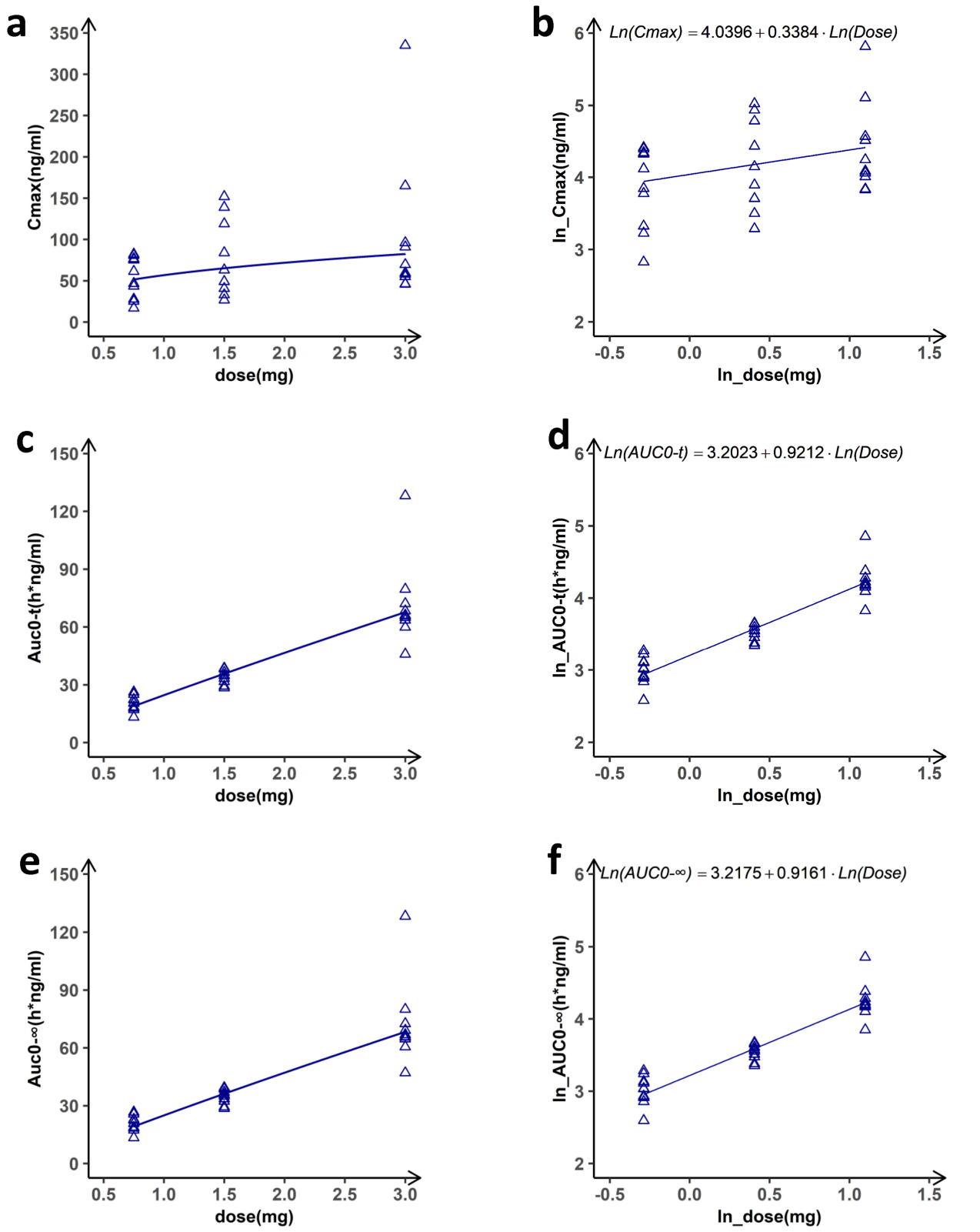

Figure 4 Main PK parameters versus dose. (**a**) Dose(mg) versus C_{max}(ng/mL) (**b**) Logarithmic plot of dose versus C_{max} (**c**) Dose(mg) versus AUC_{0-t}(ng/mL) (**d**) Logarithmic plot of dose versus AUC_{0-t} (**e**) Dose(mg) versus $AUC_{0-\infty}$(ng/mL) (**f**) Logarithmic plot of dose versus $AUC_{0-\infty}$.

Table 4 Contrast of PK Parameters in the 1.5 Mg Group Between This and Previous Studies (GeoMean)

Parameters	This study (N=10)	CP130-1003 (N=29)	CP130-1005A (N=8)
C_{max}(ng/mL)	65.969	46.7	46.9
T_{max}(h)	0.034	0.167	0.03
AUC_{0-t} (ng·h/mL)	34.249	43.3	28.4
$AUC_{0-\infty}$(ng·h/mL)	34.668	43.8	30.3
V_z(L)	116.961	-*	92.3
CL(L/h)	43.267	34.3	49.5
$t_{1/2}$(h)	1.874	1.93	1.61

Note: *No relevant data.

Table 5 Contrast of PK Parameters in the 3.0 Mg Group Between This and Previous Studies (GeoMean)

Parameters	This study (N=10)	CP130-1002 (N=6)	CP130-1003 (N=30)	CP130-1005A (N=9)
C_{max}(ng/mL)	81.914	55.56	75.9	74.7
T_{max}(h)	0.083	0.083	0.167	0.03
AUC_{0-t} (ng·h/mL)	69.096	72.748	81.2	56.5
$AUC_{0-\infty}$(ng·h/mL)	69.783	73.399	81.8	60.5
V_z(L)	129.273	-*	-*	92.1
CL(L/h)	42.991	40.876	36.7	49.6
$t_{1/2}$(h)	2.084	3.144	1.9	1.55

Note: *No relevant data.

Table 6 Comparison of PK Blood Collection Time Points

	Before Administration	Time 0[c]	5 min	10 min	15 min	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	12 h	24 h	48 h
This study[a]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
CP130-1002[a]	X	X	X		X	X	X	X		X		X	X	X	
CP130-1003[b]	X	X		X		X	X	X	X	X		X	X	X	
CP130-1005A[b]	X	X	X		X	X	X	X	X	X	X				

Notes: The CP130-1005A study employed a repeated dosing regimen, administering doses every 6 hours. For the purpose of this comparison, only the blood collection time points within the first 6-hour period post-initial dosing are included. [a]The post-dose time point is the time after the start of the study drug infusion. [b]The post-dose time point refers to the time after the end of the study drug infusion. [c]"time 0" is 2 minutes after the start of the study drug infusion or at the end of the study drug infusion.

Table 7 Comparison of "Time 0" PK Blood Collection Time Point Between This and Previous Studies

"time 0"	This study	CP130-1002	CP130-1003	CP130-1005A
Specify the acquisition time point	Immediately after the end of infusion	Immediately before the end of the infusion	Before the end of infusion	Within 30s before the end of infusion
Actual average acquisition time point	2.04 min	1.75 min	1.5 min	-*

Note: *No relevant data.

depression, slowing of gastrointestinal motility, and sedation.[23–28] This open PK study, involving a single intravenous dose of oliceridine fumarate infused at a constant rate over 2 minutes, aimed to elucidate the safety, tolerability, and PK characteristics of this drug in a Chinese cohort.

In our study we observed similarities with the United States study by comparing the values of PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, V_z, CL and $t_{1/2}$) in the present study with those in the United States trials using a 2 min infusion time

Table 8 Treatment-Emergent Adverse Events

SOC/PT	0.75 mg(N=12)		1.5 mg(N=10)		3.0 mg(N=10)		Total(N=32)	
	Events	Cases (%)	Events	Cases (%)	Events	Cases (%)	Events	Cases (%)
Total	22	8(66.7%)	34	9(90.0%)	44	10(100.0%)	100	27(84.4%)
Nervous system disorders	4	2(16.7%)	13	7(70.0%)	20	10(100.0%)	37	19(59.4%)
Lethargy	2	2(16.7%)	4	4(40.0%)	6	6(60.0%)	12	12(37.5%)
Dizziness	2	2(16.7%)	7	7(70.0%)	3	3(30.0%)	12	12(37.5%)
Vertigo	0	0(0.0%)	0	0(0.0%)	6	6(60.0%)	6	6(18.8%)
Hypoesthesia	0	0(0.0%)	2	2(20.0%)	3	3(30.0%)	5	5(15.6%)
Sleepy	0	0(0.0%)	0	0(0.0%)	1	1(10.0%)	1	1(3.1%)
Pre-syncope	0	0(0.0%)	0	0(0.0%)	1	1(10.0%)	1	1(3.1%)
Various inspections	6	3(25.0%)	11	7(70.0%)	10	7(70.0%)	27	17(53.1%)
Decreased oxygen saturation	2	2(16.7%)	0	0(0.0%)	5	5(50.0%)	7	7(21.9%)
Decreased systolic blood pressure	0	0(0.0%)	0	0(0.0%)	2	2(20.0%)	2	2(6.3%)
Decreased heart rate	0	0(0.0%)	1	1(10.0%)	0	0(0.0%)	1	1(3.1%)
Elevated heart rate	0	0(0.0%)	0	0(0.0%)	1	1(10.0%)	1	1(3.1%)
Elevated blood pressure	0	0(0.0%)	3	1(10.0%)	0	0(0.0%)	3	1(3.1%)
Systemic reactions and various reactions at the administration site	9	6(50.0%)	5	5(50.0%)	5	5(50.0%)	19	16(50.0%)
Feelings of heat	3	3(25.0%)	4	4(40.0%)	2	2(20.0%)	9	9(28.1%)
Relaxed feeling	6	6(50.0%)	0	0(0.0%)	2	2(20.0%)	8	8(25.0%)
Asthenia	0	0(0.0%)	1	1(10.0%)	1	1(10.0%)	2	2(6.3%)
The skin and subcutaneous tissue disorders	0	0(0.0%)	2	2(20.0%)	6	4(40.0%)	8	6(18.8%)
Pruritus	0	0(0.0%)	0	0(0.0%)	4	4(40.0%)	4	4(12.5%)
Sweaty	0	0(0.0%)	2	2(20.0%)	1	1(10.0%)	3	3(9.4%)
Flush	0	0(0.0%)	0	0(0.0%)	1	1(10.0%)	1	1(3.1%)
Gastrointestinal disorders	3	3(25.0%)	1	1(10.0%)	2	2(20.0%)	6	6(18.8%)
Nausea	1	1(8.3%)	1	1(10.0%)	2	2(20.0%)	4	4(12.5%)
Dry mouth	2	2(16.7%)	0	0(0.0%)	0	0(0.0%)	2	2(6.3%)
Respiratory system, chest, and mediastinum disorders	0	0(0.0%)	1	1(10.0%)	1	1(10.0%)	2	2(6.3%)
Dyspnea	0	0(0.0%)	1	1(10.0%)	1	1(10.0%)	2	2(6.3%)
Cardiovascular system disorders	0	0(0.0%)	1	1(10.0%)	0	0(0.0%)	1	1(3.1%)
Palpitations	0	0(0.0%)	1	1(10.0%)	0	0(0.0%)	1	1(3.1%)

Abbreviation: SOC/PT, systematic organ classification and preferred term.

dosing regimen at the same administered doses (1.5 mg to 3.0 mg). Within the 0.75 mg to 3.0 mg dosage range, oliceridine fumarate injection exhibited low variability in its AUC values (AUC_{0-t}: 11.22% to 26.39%; $AUC_{0-\infty}$: 11.38% to 28.55%), demonstrating a dose-proportional increase. The range of these AUC parameter values closely paralleled those observed in the original trials. In that study, most TEAEs were mild and related to the test drug. These TEAEs were generally consistent with the common adverse effect profile following opioid administration and the type and extent of TEAEs in the United States trials (eg nausea, vomiting, dizziness, headache, constipation, pruritus, and hypoxia),[23,25] with no unintended TEAEs occurring. The incidence of TEAEs appeared dose-dependent, with the 1.5 mg and 3.0mg dose groups exhibiting a greater number of TEAEs compared to the 0.75mg group, and with the latter exhibiting more TEAEs than the former. Importantly, no serious adverse events or adverse events leading to study discontinuation occurred, reaffirming the consistency of our findings with the original trials. These similarities underscoring the consistency of oliceridine 's PK profile,[23,25] there was little difference in the composition of oliceridine fumarate injection used in this study and oliceridine used in the United States trials, while the drug's PK parameters (AUC, V_z, CL, and $t_{1/2}$) and adverse effects of the drug do not have race sensitivity, food effects, low bioavailability, and high inter-

individual variability in bioavailability concerns. But more clinical trials or randomized double-blind trials are needed to confirm this.

The difference is that the C_{max} values in this study were slightly higher than the C_{max} values in the United States trials for the same dose and administration time.[23,25] This may be due to the difference in time point of blood sample collection. In the present study, the first time point of blood sample collection after the start of drug infusion (immediately after the end of infusion) was done after the end of drug administration, and the actual average time of collection was 2.04 min after the start of drug administration. In the original 1002 trial(CP130-1002), the average collection time was 1.75 min post-infusion start, while the 1003(CP130-1003) and 1005A(CP130-1005A) trials set this time slightly earlier, at 1.5 min and within 30 seconds before infusion completion, respectively. This timing difference is significant: in the original study, the infusion was not entirely complete at "time 0", meaning a portion of the drug had not yet entered the body. Conversely, in this study, the entire drug dose was administered by "time 0". This discrepancy likely accounts for the observed slight variation in C_{max} in this study compared to the original data. Moreover, both studies exhibited high variability in C_{max}, with this study ranging from 58.47% to 71.03% and the original 1002,1003, and 1005A trials showing variabilities of 12.27% to 39.62%, 65.7% to 70.4%, and 73.4% to 94.6%, respectively. Such significant individual variability is another potential factor contributing to the C_{max} discrepancies between this and the original studies.Also, ethnicity is a potential factor. C_{max} and other PK parameters can vary between ethnicities.

We acknowledge some limitations of this study. Being an open-label, single-dose study, it lacked both a comparator and a multiple-dose phase. As a novel opioid analgesic, oliceridine fumarate injection shows promise in managing suitable for alleviating acute postoperative pain, breakthrough pain, and acute exacerbations of chronic pain. Its profile, characterized by a rapid onset and shorter duration of action, surpasses that of morphine in efficacy and has fewer side effects. While it appears well-suited for clinical application, its effectiveness and safety necessitate further validation. Continuous monitoring of its effects is critical to ensure its optimal use in clinical settings and to effectively address complex clinical challenges.

Conclusion

The results of this study affirm that oliceridine exhibits PK parameters and characteristics within the Chinese population that are comparable to those observed in the original trial in the United States, particularly across the 0.75 mg to 3.0 mg dose range. Administered as a single intravenous dose at a constant rate over 2 min to patients with chronic non-cancer pain, oliceridine was found to be safe and well tolerated. Notably, there were no reported SAEs, and the nature and severity of TEAEs closely mirrored those observed in the original trials, with no unexpected TEAEs. This study demonstrates the acceptable safety profile, tolerability, and pharmacokinetic suitability of oliceridine fumarate injection, reinforcing its potential for continued clinical development and application in the Chinese patient population.

Data Sharing Statement

The clinical raw data in this paper will be available upon reasonable request through an e-mail to the corresponding author (Guoping Yang).

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Disclosure

The authors declare no conflicts of interest in this work.

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