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Novel Anesthetic Agent: Ciprofol an Alternative of Propofol- An Updated Review Article.

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Abstract:

Background: Anesthesia is crucial for minimizing pain and stress during medical procedures, with intravenous general anesthesia being the most common method due to its rapid onset, ease of control, and low irritability. Propofol, a widely used anesthetic, is known for its quick action but also for several adverse effects such as nausea, headaches, and cardiovascular issues. Ciprofol, a novel anesthetic agent, was introduced to address the limitations of propofol, including reducing the frequency of adverse drug reactions (ADRs).

Aim: This article provides an updated review of ciprofol, evaluating its structural features, pharmacodynamics, pharmacokinetics, and clinical effectiveness as an alternative to propofol for sedation and anesthesia.

Methods: A review of preclinical and clinical trials, including Phase I, II, and III studies, is conducted to compare ciprofol's sedative and anesthetic properties with those of propofol. Pharmacological interactions and safety profiles were assessed in various clinical settings.

Results: Ciprofol has demonstrated superior target selectivity and affinity for the GABAA receptor compared to propofol, leading to more efficient sedation and anesthesia at lower doses. Clinical trials in procedures such as colonoscopy, gastroscopy, and bronchoscopy show that ciprofol provides faster onset, comparable sedation duration, and higher patient satisfaction relative to propofol. The drug also exhibits a lower incidence of adverse effects like cardiovascular and respiratory depression.

Conclusion: Ciprofol is a promising alternative to propofol, offering a safer profile with fewer ADRs and more effective sedation at lower doses. Its clinical application in sedation for gastrointestinal endoscopy and anesthesia in surgeries shows promising results, positioning it as a potential mainstay in anesthesia practice.

Keywords: Ciprofol, propofol, anesthesia, sedation, GABAA receptor, clinical trials, pharmacodynamics, pharmacokinetics.

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Introduction:

Anesthesia is essential for reducing stress and pain during medical operations, which guarantees that exams and surgeries go smoothly [1]. Because of its quick onset, low irritability, and simplicity of control, intravenous general anesthesia is the most widely used anesthetic technique [2, 3]. A common short-acting intravenous anesthetic, propofol functions as an agonist and allosteric potentiator of the gamma-aminobutyric acid type A (GABAA) receptor [4]. By decreasing neuronal excitability and strengthening GABA's inhibitory activity in the central nervous system, it produces sedative and anesthetic effects [5, 6]. Propofol's good pharmacodynamics and pharmacokinetics (PK), which include a rapid onset of anesthesia, a rapid recovery, low respiratory irritation, and negligible residual effects, support its therapeutic use [7, 8]. Despite its advantages, propofol can result in a number of adverse drug reactions (ADRs), including as headaches, nausea, vomiting during resuscitation, cardiovascular and respiratory depression, local pain during induction, and hypotension from a quick infusion [9–12]. Furthermore, despite being uncommon, propofol infusion syndrome (PRIS) is a potentially lethal adverse drug reaction (ADR) that can cause organ failure, metabolic abnormalities, and even death [13–15]. The structure of propofol has been altered in an attempt to create novel molecules with a lower frequency of adverse drug reactions (ADRs). 2017 saw the initial release of ciprofol (HSK3486), which was created by Haisco Pharmaceutical Group Co., Ltd. (Chengdu, China) [16, 17]. Ciprofol has the molecular structure (R)-2-(1-cyclopropyl ethyl)-6-isopropylphenol. Following a priority assessment, the China National Medical Products Administration (NMPA) approved ciprofol on December 15, 2020, for use as a sedative during gastrointestinal endoscopy. Since then, it has been authorized for the induction and maintenance of general anesthesia as well as for sedation during bronchoscopy. Sedation during intensive care was added to its list of indications by a recent NMPA approval. The effectiveness and safety of ciprofol for sedation/anesthesia in gynecological outpatient procedures has been assessed in a Phase III clinical trial conducted in China, and this indication is presently being reviewed. It is anticipated that ciprofol's clinical uses would increase. The chemical structure, pharmacodynamics, and PK characteristics of ciprofol are described in this publication along with an overview of the safety and effectiveness assessments.

Structural Features and Mechanisms

GABAA receptors react to anesthetics in a stereoselective manner [18]. A 2,6-disubstituted phenol makes up the fundamental structure of traditional short-acting intravenous anesthetics. It binds to the GABAA receptor to induce anesthetic effects. While ciprofol adds a cyclopropyl group to the side chain, propofol, a common anesthetic, shares this basic structure (**Figure 1**). By breaking the original structure's symmetry, increasing the spatial effect, and decreasing the parent structure's lipophilicity, this change produces a chiral center and a stereoselective product. Because of these modifications, ciprofol has a greater receptor affinity than propofol. Additionally, ciprofol's R-enantiomer is more potent and stereoselective for the GABAA receptor than its S-isomer. Ciprofol exhibits better target selectivity than propofol, indicating a higher pharmacological action, according to a radioligand-binding experiment [16]. Both propofol and ciprofol function as direct agonists of the GABAA receptor and positive allosteric modulators in terms of receptor interaction. Ciprofol can cause chloride inflow by competitively binding to butylbicyclophosphorothionate and t-butylbicycloorthobenzoate at the chloride channels of GABAA receptors, according to whole-cell patch-clamp investigations and competitive binding assays [19]. This chloride inflow causes nerve cell membranes to become hyperpolarized, raises intracellular chloride levels,

and stimulates GABAergic neurons, which inhibits the central nervous system and produces sedative and anesthetic effects.

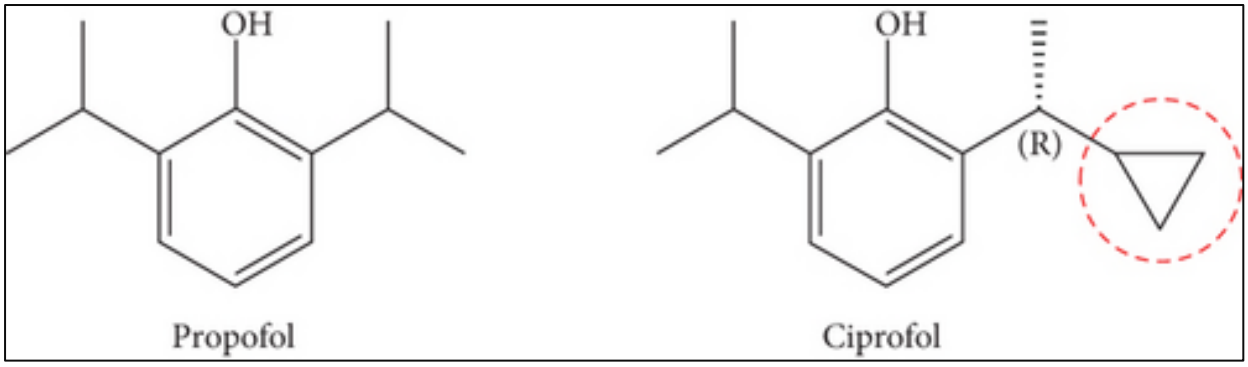

Figure 1: Structure of Propofol and Ciprofol.

Pharmacodynamics

Preclinical Studies:

Ciprofol's sedative and anesthetic effects have been confirmed in animal models. At dosages ranging from 2.0 mg/kg and above, the loss of righting reflex (LORR), a commonly used behavioral marker for assessing the hypnotic effects of anesthetic drugs [20,21], was seen in all participants, with durations directly corresponding to the dose given. At 10 minutes (HD10) and 50 minutes (HD50) post-LORR, the dosages of ciprofol needed to produce hypnotic effects in rats were roughly one-fifth and one-sixth of those necessary for propofol, respectively. Ciprofol's therapeutic index was somewhat higher than propofol's, and its median lethal dose (LD50) was a fourth of propofol's. These results highlight the unique target selectivity and affinity advantages of ciprofol, indicating that it may be able to provide therapeutic effects comparable to those of propofol at significantly lower dosages.

Clinical Trials

Numerous clinical studies have further supported ciprofol's sedative and anesthetic effectiveness, as seen in the section that follows. Eight healthy participants received ciprofol intravenously in the first phase of clinical trials at a dose of 1 mg/kg/h for 0.5 hours and then 0.4 mg/kg/h for an additional 3.5 hours. The sedative effects lasted an average of 12.58 minutes (mean ± SD: 2.05 ± 0.45). These results were similar to those of propofol, which yielded a sedation time of 10.88 ± 1.62 minutes at 5 mg/kg/h for 0.5 hours and 2 mg/kg/h for 3.5 hours, with no statistically significant changes in alertness or sedation satisfaction ($p > 0.05$ for both) [23]. Ciprofol at 0.4 mg/kg produced sedation lasting 1.6 ± 0.5 minutes in phase IIa clinical trials centered on colonoscopy sedation, with alertness times significantly different from those of propofol, which was given at 2 mg/kg, demonstrating a significantly lower sedation satisfaction score ($p < 0.05$) [24]. In other trials, ciprofol dosages of 0.4 mg/kg during colonoscopy procedures similarly showed quicker onset times, and patients expressed greater pleasure with sedation compared to propofol ($p < 0.05$) [24]. In comparison to propofol, which was administered at 1.5 mg/kg, ciprofol at 0.4 mg/kg produced quick sedation with considerably higher alertness ($p < 0.001$) and sedation satisfaction, according to phase III trials investigating deep sedation for gastroscopy and colonoscopy procedures [25]. Ciprofol's therapeutic superiority was highlighted by another Phase III trial that used a 0.4 mg/kg dose for fiber-optic bronchoscopy procedures. The experiment showed shorter induction periods and improved patient satisfaction when compared to propofol [26]. The safety and effectiveness of ciprofol were further validated by later trials on the induction and maintenance of anesthesia during elective surgeries. Despite different dose protocols, comparative results showed favorable responses in terms of sedation duration and satisfaction relative to propofol [27, 28]. In intensive care unit patients receiving mechanical breathing, the medication's capacity to maintain sufficient sedation and speedy recovery times was also demonstrated [29, 30]. Together, these results highlight ciprofol's clinical effectiveness as a substitute for propofol in a range of sedation and anesthetic contexts.

Phase I Clinical Trials

The safe and efficient intravenous dosing range for ciprofol emulsion, including its single loading dose, initial maintenance dose, and future maintenance dose ranges for prolonged sedation and anesthesia, was determined in large part by phase I clinical trials. The suggested dose modification ranges were also determined by these trials. One phase I experiment examined the anesthetic effectiveness of ciprofol in 24 healthy Chinese participants. Following the administration of 0.4, 0.6, and 0.9 mg/kg doses of ciprofol, the study showed that the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score rapidly decreased, with corresponding occurrences of loss of verbal response (LORverbal) reaching 83.3%, 100%, and 100%, respectively [22]. Recovery of verbal response (RORverbal), LORverbal, MOAA/S ≤ 1 (deep sedation), and return of responsiveness (talert) all took longer as the dosage increased. Furthermore, the durations during which the three doses' bispectral indices (BIS) were less than 60 (i.e., unresponsive to spoken stimuli) were 6, 8, and 12 minutes. It was shown that these decreased in a dose-dependent way. Significant dosage dependence was seen in the median times for orientation recovery, which were 9.0, 11.0, and 19.5 minutes, and the median times until loss of the eyelid reflex, which were 1.7, 1.5, and 1.0 minutes for the three doses, respectively. There were no appreciable changes between the Modified Quality of Recovery-9 (QoR-9) scores before and after ciprofol administration, indicating a satisfactory recovery. Because doses between 0.4 and 0.9 mg/kg were well tolerated, it was suggested that future Phase II studies use a dose higher than 0.4 mg/kg. The pharmacodynamics and pharmacokinetics (PK) of continuous ciprofol infusion were further investigated in a phase I experiment (n = 64). Regarding the time to commencement of sedation or recovery following anesthesia, the experiment did not find any statistically significant differences between propofol and ciprofol. Propofol had a slightly longer duration of sedation than ciprofol, although both medications' pharmacodynamic properties were similar. According to these results, ciprofol is not less effective, safe, or tolerable than propofol when used for long-term sedation. A dose modification recommendation for additional research was suggested based on the tolerance results of the experiment. This proposal included a loading dose range of 0.1–0.2 mg/kg for a 1–5 minute infusion, followed by maintenance doses between 0.3 mg/kg/h and 0.06–0.8 mg/kg/h [23].

Phase II and III Clinical Trials

Phase II and III clinical trials evaluated the efficacy and safety of ciprofol in comparison to propofol, further confirming its appropriate dosing in various clinical settings.

Gastroscopy and Colonoscopy:

The effectiveness and safety of ciprofol for sedation during colonoscopy procedures were examined in multicenter Phase IIa and IIb trials [24]. Similar to propofol (2.0 mg/kg), ciprofol at doses of 0.2–0.5 mg/kg had a 100% success rate for colonoscopy insertion, according to phase IIa (n = 64) data. The 0.5 mg/kg ciprofol group's colonoscopy insertion time was similar to that of the propofol group (1.2 ± 0.4 minutes vs. 1.2 ± 0.6 minutes). With 100% success rates for colonoscopy insertion, the Phase IIb trial (n = 94) subsequently indicated that the suggested dosages of 0.4 mg/kg and 0.5 mg/kg were optimum. Ciprofol and propofol had comparable recovery periods; however, anesthesiologists gave 0.5 mg/kg ciprofol a higher satisfaction rating (9.5 ± 0.8) than 0.4 mg/kg ciprofol (9.2 ± 1.0) and propofol (9.2 ± 0.9) ($P < 0.05$). These findings proved that ciprofol is a safe and effective sedative and anesthetic during colonoscopies. The relative effects of ciprofol and propofol in causing deep sedation during gastroscopy and colonoscopy were evaluated in Phase III clinical studies carried out in China (n = 30 for gastroscopy and 259 for colonoscopy) [25]. With a 100% success rate for gastroscopy and a 99.2% success rate for colonoscopy in the propofol group, both groups displayed comparable success rates. While ciprofol patients took longer to become fully alert and to be discharged than propofol patients (7.4 ± 3.1 minutes vs. 6.0 ± 2.1 minutes, $P < 0.001$), the induction times, insertion times, and success rates were similar. Nonetheless, ciprofol (9.9 ± 0.4) was more

patient-satisfied than propofol (9.7 ± 0.7) (P = 0.001). The success rates during both colonoscopies and gastroscopies showed that 0.4 mg/kg of ciprofol was not inferior to 1.5 mg/kg of propofol.

Fiber-Optic Bronchoscopy

Ciprofol's effectiveness, safety, and PK were further investigated in a Phase III trial that included 267 patients undergoing fiber-optic bronchoscopy [26]. All individuals in the ciprofol (0.4 mg/kg) and propofol (2.0 mg/kg) groups achieved deep sedation or general anesthesia, indicating a 100% success rate. The majority of patients underwent the procedure without needing a top-up dose, and the two groups' times for successful anesthetic induction and insertion were comparable. While the duration to full alertness and discharge with ciprofol was marginally longer (8.50 vs. 6.00 minutes, P = 0.012; 13.00 vs. 9.87 minutes, P = 0.002, respectively), patient and anesthesiologist satisfaction levels were similar. This multicenter, randomized, noninferiority study demonstrated that ciprofol had a decreased incidence of injection-related discomfort while offering similar anesthetic and sedative effects to propofol.

General Anesthesia in Elective Surgery:

Ciprofol's efficacy and safety in inducing and maintaining general anesthesia in elective surgical patients (n = 46) were assessed in a phase II clinical trial [27]. Forty of these individuals were randomized to receive either propofol or ciprofol in a 3:1 ratio, and the other six received a combination of the two drugs. All three groups' anesthesia induction and maintenance outcomes showed a 100% success rate, requiring no additional dosages or rescue treatments. This strong result implies that ciprofol, even when started with a different anesthetic drug, has significant efficacy in individuals having elective procedures. Additionally, the ciprofol group's induction onset time (0.4 mg/kg) was similar to that of the propofol group (2.0 mg/kg), and both groups were able to successfully induce induction within one minute. For a similar percentage of patients (13.3% vs. 10.0%, P = 1.000), the ciprofol group maintained BIS values within the target range of 40-60 during the maintenance phase. The length of BIS values within this range was similar for both groups (69.9 ± 24.7% vs. 70.5 ± 18.2%, P = 0.948). Furthermore, there was no significant difference between the ciprofol and propofol groups in terms of recovery metrics, such as the amount of time it took to return to full alertness after stopping anesthetic medications (all P > 0.05). While anesthesiologists gave ciprofol a slightly higher satisfaction rating during induction, they gave it a similar rating to propofol during anesthesia maintenance [27]. In a later phase III experiment, 176 patients undergoing elective surgery were given either propofol or ciprofol to induce general anesthesia [28]. In terms of inducing anesthesia, both groups were 100% successful, proving that ciprofol is not less effective than propofol. While both groups stayed within one minute, the mean induction times for general anesthesia and loss of eyelash reflexes were marginally higher for ciprofol (0.91 and 0.80 minutes) than for propofol (0.80 and 0.71 minutes). For ciprofol and propofol, the average exposure levels were 26.0 mg and 121.8 mg, respectively. Furthermore, ciprofol maintained stability during anesthesia by exhibiting a similar pattern of BIS alterations to propofol. With mean scores of 10.9 for ciprofol and 10.8 for propofol, anesthesiologists evaluated both medications similarly, with no discernible distinctions between the two. Ciprofol is a viable option for elective surgery when the combined data from the two clinical trial phases are considered.

Sedation during Intensive Care Units (ICU):

Ciprofol's safety, effectiveness, and pharmacokinetic characteristics for sedation in patients in intensive care units on mechanical ventilation were examined in a multicenter, open-label, randomized phase II trial (n = 39) carried out in China [29]. In order to maintain a desired sedation depth (RASS scores between -2 and +1), the patients were given a loading dose of ciprofol (0.1-0.2 mg/kg) over 0.5-5.0 minutes, followed by a maintenance infusion at a rate of 0.3 mg/kg/h for 6-24 hours. A loading dose of 0.5–1 mg/kg and a maintenance infusion of 1.5 mg/kg/h were used for propofol, in contrast. The median duration of sedation for both the propofol and ciprofol groups was 60.0 minutes. Both groups experienced similar rates of sedation-related and drug-related treatment-emergent adverse events (TEAEs), such as sinus bradycardia (3.8% vs. 7.7%, P = 1.000) and hypotension (7.7% vs. 23.1%, P = 0.310). According to these

results, ciprofol and propofol are similar in terms of patient tolerance, safety, and effectiveness in intensive care unit (ICU) settings that use mechanical ventilation. With the hope of fewer problems in intensive care unit patients, a follow-up phase III trial (n = 135) attempts to further validate the effectiveness of ciprofol in contrast to propofol [30]. Although the results of this trial have not yet been published, the approval of ciprofol for sedation in the intensive care unit later on suggests that the results are positive.

Phase IV Clinical Trials

Ciprofol's therapeutic efficacy was further confirmed in clinical settings using the dosage schedule outlined in the National Medical Products Administration-approved medication instructions (NMPA). In a study of 96 clinical patients undergoing painless gastroenteroscopy, Chen et al. compared the effects of ciprofol and propofol on intraoperative adverse responses, surgical techniques, resuscitation attempts, and patient satisfaction. This study emphasized the therapeutic benefits of ciprofol and supported the results of other investigations. Significantly, the ciprofol group experienced less side effects (53.19%) than the propofol group (63.26%), with a statistically significant difference ($P < 0.05$). One minute after delivery, however, the ciprofol group's mean arterial pressure (MAP) was considerably lower (92.11) than the propofol group's (98.22) ($P = 0.011$). Furthermore, after three minutes of delivery, the ciprofol group's diastolic blood pressure (DBP) was somewhat lower (71.75 vs. 75.22), but the difference was not statistically significant ($P = 0.08$). Ciprofol or propofol were used to produce general anesthesia for gynecologic surgery in 120 female patients between the ages of 18 and 60 in a different prospective, double-blind, single-center study. Comparable efficacy was indicated by the study's lack of significant differences between the two medications in terms of induction success rates, induction length, time for the eyelid reflex to diminish, or tracheal intubation ($P > 0.05$ for all comparisons). Nonetheless, the ciprofol group experienced a considerably lower total incidence of adverse responses (20%) than the propofol group (48.33%) ($P = 0.0019$). [31] [32].

Pharmacokinetics

When ciprofol was administered intravenously to rats, it was widely distributed over a variety of tissues and quickly removed from the majority of them, which lessened the effects of post-anesthesia. Ciprofol was shown to be five times more concentrated in tissue in the kidneys, ovary, fat, skin, and adrenal gland than in plasma, and 3.2 times more concentrated in the brain than in plasma. These findings suggest that ciprofol successfully crosses the blood-brain barrier. In accordance with plasma levels, the majority of tissues attained their highest concentration (Tmax) in 4 minutes. With the exception of fat, skin, bladder, and uterus, the residual concentration in the majority of tissues was less than 10% of the peak (Cmax) following 240 minutes of administration. Additionally, ciprofol showed broad plasma protein binding; in human plasma, the binding rate reached 95% within the 80–1200 ng/mL concentration range [19][33]. According to a pharmacokinetic study, Tmax happened two to three minutes after a single intravenous dosage of C14-labeled ciprofol (0.4 mg/kg) in healthy volunteers, and it dropped to levels close to baseline in about ten minutes. Ciprofol is mostly metabolized in the liver by the enzymes uridine diphosphate-glucuronyltransferase (UGT) and cytochrome P450 (CYP) 2B6. Oxidation is the most common metabolic process, followed by conjugation with sulfuric and glucuronic acids. A ciprofol-glucuronic acid conjugate was found to be the primary metabolite, and a mono-oxidized ciprofol-glucuronic acid conjugate was shown to be the secondary metabolite. Urine excretion accounts for the majority of ciprofol and its metabolites (84.6%), with feces accounting for a smaller portion (2.65%) [34]. The following findings were reported from a study that assessed the pharmacokinetic characteristics of ciprofol in healthy subjects under several delivery regimes (single-dose administration, sequential maintenance dosing after the initial dosage, and maintenance dosing after the loading dose): The maximum plasma concentration (Cmax) was 1,330 ng/mL after a single dosage of 0.4 mg/kg, and Tmax happened after 2.0 minutes. The apparent volume of distribution (Vd) was 4.3 L/kg, the clearance (CL) was 1.47 L/h/kg, and the elimination half-life (T1/2) was 2.09 hours. After a single dose of ciprofol, these values show a quick onset of activity and a short duration of impact. Both Tmax and T1/2 were considerably prolonged, with a greater Vd, when maintenance dosing was administered after the first or loading dosage. Accordingly, ciprofol may be used in clinical settings as

a continuous intravenous infusion to maintain sedation for a maximum of 12 hours [22][23]. A phase II clinical investigation assessing the induction and maintenance of general anesthesia in patients undergoing elective surgery showed that the pharmacokinetic characteristics of ciprofol and propofol are similar. While propofol concentrations in the propofol group exhibited a similar pattern throughout the induction period, the plasma concentration of ciprofol in the propofol+cipofo group during the anesthesia maintenance phase was consistent with that in the ciprofol-only group. But compared to ciprofol, propofol showed four to five times greater drug exposure. While Tmax (0.17 hours vs. 0.11 hours) and clearance (CL) values (1.0 ± 0.4 L/h/kg vs. 1.1 ± 0.3 L/h/kg) were almost the same for both medications, Ciprofol showed slightly shorter T1/2 (13.0 ± 10.9 hours vs. 19.6 ± 2.2 hours) and Vd (18.0 ± 18.8 L vs. 32.0 ± 9.3 L) [27].

Safety Profile of Ciprofol

Evaluations of ciprofol's genotoxicity and reproductive toxicity showed no serious issues. The chromosome aberration test with Chinese hamster lung fibroblasts, the mouse bone marrow micronucleus test, and the Ames reverse mutation test with Salmonella typhimurium all produced negative genotoxicity results. Additionally, testing for perinatal developmental toxicity, embryo-fetal developmental toxicity, and rat fertility and early embryonic development toxicity did not reveal any discernible reproductive harm. After ciprofol injections at dosages of 1, 2, or 4 mg/kg, telemetry tests in beagle dogs showed that all treatment groups experienced temporary tachycardia within two minutes after the injection. The animals' stress response after injection may be the cause of the 88%, 106%, 134%, and 169% increases in heart rates. Interestingly, within an hour of ciprofol treatment, the corrected QT interval (QTc) was lengthened in a dose-dependent way, but there was no discernible change in respiration rate. Additionally, there was a noticeable decline in body temperature, with the 4 mg/kg dosage group experiencing the largest dip. Furthermore, the 2 mg/kg and 4 mg/kg groups showed notable drops in blood pressure, with mean arterial pressure falling by 21.3% and systolic and diastolic blood pressures falling by 18.8% and 23.3%, respectively. Following their recovery, the animals showed no signs of any long-term damage. Ciprofol is typically well tolerated, according to data from clinical trials. Hypotension, bradycardia, apnea, respiratory depression, hypoxia, and injection site pain are examples of common adverse drug reactions (ADRs). Phase IIa trials including sedation or anesthesia for colonoscopy and phase III trials using deep sedation during gastroscopy and colonoscopy reported five major adverse drug reactions (ADRs), but these were isolated cases. Most of the other ADRs were mild to moderate and went away with little help. Crucially, save from one case of epilepsy in a phase II study of sedation in intensive care unit patients on mechanical breathing, there were no reports of ADRs that resulted in death, and no patients left the studies because of ADRs. There were no dose-dependent ADRs. Treatment-emergent adverse events (TEAEs) were less common with ciprofol (0.4 mg/kg) than with propofol (2 mg/kg) [24, 25]. Ciprofol typically showed a lower incidence of injection pain than propofol, according to a comparison of the reported TEAEs across multiple clinical trials. This decrease is explained by ciprofol's lower free drug concentration, which makes it less likely than propofol to produce pain-inducing chemicals [35]. Furthermore, because ciprofol is more potent, its plasma concentration is much lower, which helps to lessen injection pain. In contrast, the increased concentration of the free drug in the propofol solution may produce pain-inducing chemicals or directly contact nerve terminals to generate pain [36].
Propofol is known to enhance fat transport, which raises triglyceride levels in relation to hypertriglyceridemia, particularly in intensive care unit patients.

On the other hand, ciprofol's 1% solution has a substantially lower fat content, which could potentially lessen the risk of hypertriglyceridemia. Nevertheless, additional investigation is required to validate the effect of ciprofol on triglyceride levels. Even with these safety benefits, muscle fasciculation is still a possibility, especially at higher dosages. Muscle fasciculation was seen in a dose-dependent fashion in a phase I clinical study, with incidences of 33.3%, 33.3%, and 83.3% at dosages of 0.4, 0.6, and 0.9 mg/kg, respectively [22]. Additional studies, such as those for colonoscopy sedation and anesthesia, found that ciprofol was more likely than propofol to cause muscular fasciculation. Interestingly, in a phase IIa trial, the 0.4 mg/kg ciprofol group experienced a greater incidence of muscle fasciculation than the 2.0 mg/kg propofol group (4.5% vs. 0%) [24]. At different ciprofol dosages (0.2, 0.3, 0.4, and 0.9 mg/kg), fasciculation

was seen in later studies; however, the mechanism behind this event is still unknown and needs more research. Phase II and III studies reported one case of epilepsy and one case of myoclonus, respectively, underscoring the necessity for more investigation into the connection between ciprofol and muscular fasciculation [28, 29]. In conclusion, ciprofol is linked to a lower incidence of respiratory depression, less injection pain, and a lower lipid load, even though it has similar effects on blood pressure and heart rate to propofol. Muscle fasciculation is still a possible side effect, though, and needs more research.

Special Population

Ciprofol's pharmacokinetic (PK) and pharmacodynamic (PD) characteristics, as well as its safety profile, were assessed in Chinese individuals who were not elderly and in good health [40]. A single intravenous dosage of ciprofol at 0.2, 0.3, and 0.4 mg/kg was administered to each of the three experimental groups, which consisted of 24 elderly participants (ages 65-73) who were randomly allocated. On the other hand, 0.4 mg/kg was given to the nonelderly control group (n = 8, ages 21–44). The results showed that while there were no appreciable variations in the distribution or elimination of the drug across the groups, the senior group's plasma exposure levels of ciprofol rose with the dosage. Age did not appear to have a significant impact on plasma ciprofol exposure, as indicated by the similar PK profiles of ciprofol (at 0.4 mg/kg) in both groups. With average free fractions of 0.8%, 0.8%, 0.8%, and 0.9%, and plasma protein binding rates of 99.2%, 99.2%, 99.2%, and 99.1%, respectively, there were no statistically significant changes between the experimental and control cohorts [40]. The senior group (0.2 mg/kg) showed slightly longer periods of unconsciousness and shorter recovery times in terms of clinical effects. The elderly groups' recovery periods from 0.3 mg/kg and 0.4 mg/kg were comparable to those of the nonelderly cohort. Additionally, compared to the nonelderly group, the elderly group experienced a slightly greater rate of treatment-emergent adverse events (TEAEs), with the highest incidence occurring in the senior subgroup receiving 0.4 mg/kg. These findings support the recommendation that older patients take 0.3 mg/kg since it has similar sedative and anesthetic effects with fewer side effects.

Clinical data from Li et al. [40] and National Medical Products Administration (NMPA) Chinese product instructions for patients with hepatic and renal impairments show that mild and moderate hepatic insufficiency has little effect on ciprofol's effectiveness as determined by MOAA/S and BIS values. After a single intravenous dosage of ciprofol, safety profiles for people with mild to severe hepatic impairment were satisfactory; no withdrawals owing to adverse events or serious adverse events (SAEs) were noted. Although increased safety monitoring was advised, no dose changes were required for these patients. Similarly, because ciprofol has a high rate of protein binding, renal insufficiency has no effect on its pharmacodynamic markers. There were no SAEs or trial dropouts because of adverse events, confirming the safety of ciprofol in individuals with mild to moderate renal insufficiency. In these groups, no dose modification is necessary, similar to hepatic insufficiency. However, ciprofol is not advised for individuals who need dialysis or who have severe hepatic or renal impairments because there is little clinical data on these populations.

A comparison of ciprofol and propofol in 120 renal transplant recipients was carried out by Qin et al. [41]. According to the study, both groups' sedation success rates were 100%. In contrast to propofol, ciprofol showed a shorter time to the disappearance of the eyelash reflex and a quicker fall in BIS to 60. It also required less intraoperative sedative and had longer recovery durations (all P values < 0.001). Injection discomfort and intraoperative hypotension were also less common in the ciprofol group (P < 0.01), although other adverse responses did not differ significantly. The safe use of ciprofol in kidney transplant patients was supported by the remarkable improvement in early postoperative kidney function that both groups demonstrated, with no discernible difference in kidney recovery indicators. There is not enough clinical evidence to support the use of ciprofol in individuals younger than 18 or in women who are pregnant or nursing. Lactating women should stop nursing while receiving treatment, and healthcare professionals should carefully weigh the risks and advantages of ciprofol for expectant mothers. It is not advised to use ciprofol for sedation and anesthesia in pediatric populations until additional validation and dosage approval are finished, as propofol infusion syndrome was first documented in pediatric patients [42, 43].

Drug-Drug Interaction

Combining ciprofol with fentanyl, sufentanil, or midazolam has shown no pharmacological incompatibilities, and the results have been satisfactory. Ciprofol and low-dose sufentanil together produced a significantly lower total dosage of ciprofol, a shorter induction time ($P < 0.05$), and a significantly lower overall incidence of adverse events ($P < 0.001$) than the monotherapy group, according to a study examining the anesthetic effects of ciprofol alone or in combination with sufentanil for painless gastroscopy [44]. Moreover, the effect of esketamine in combination with either ciprofol or propofol on respiratory and hemodynamic adverse events in patients undergoing same-day bidirectional endoscopy is presently being assessed in a randomized, double-blind, placebo-controlled, multicenter clinical trial carried out in China [45]. Additionally, the study will evaluate the drug-drug interaction between ciprofol and esketamine, though the clinical trial is currently in progress and data has not yet been released. Future findings will confirm the safety of this combination in clinical practice and establish whether there are any pharmacological incompatibilities between the two medications.

Conclusion:

Ciprofol, a novel anesthetic agent introduced as an alternative to propofol, demonstrates significant advancements in anesthesia and sedation practices. The molecular modifications in ciprofol, including the addition of a cyclopropyl group and the introduction of a chiral center, enhance its affinity and selectivity for the GABAA receptor. This leads to improved pharmacological effects, allowing ciprofol to achieve the same therapeutic outcomes as propofol, but at lower doses, which translates to fewer adverse drug reactions (ADRs). The clinical trials conducted across various settings, including gastrointestinal endoscopy, bronchoscopy, and outpatient procedures, confirm ciprofol's efficacy and safety. For example, Phase II and III trials in colonoscopy and gastroscopy procedures revealed that ciprofol provides rapid sedation with a quicker onset compared to propofol, leading to better patient satisfaction. Furthermore, ciprofol's sedative effects were shown to last longer without compromising recovery times, which enhances its practical use in medical procedures. From a pharmacokinetic perspective, ciprofol's ability to produce rapid induction and recovery times, similar to propofol, ensures that patients benefit from effective sedation with minimal lingering effects. The safety profile of ciprofol is notably improved, with significantly reduced risks of cardiovascular and respiratory depression, which are common with propofol. This makes ciprofol an especially promising candidate for use in patients who are prone to complications associated with conventional anesthetic agents. In conclusion, ciprofol offers an innovative solution for the limitations associated with traditional anesthetics like propofol. With its higher receptor selectivity, reduced incidence of ADRs, and proven clinical efficacy, ciprofol is well-positioned to become a preferred anesthetic for a range of medical procedures. Future studies will continue to evaluate its long-term safety and efficacy across different patient populations and clinical settings, further solidifying its role in modern anesthesia practices.

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مقالة مراجعة محدثة: وكيل مخدر جديد: سيبروفول كبديل للبروبوفول

الملخص:

الخلفية: التخدير أمر بالغ الأهمية لتقليل الألم والتوتر أثناء الإجراءات الطبية، ويعد التخدير العام الوريدي الطريقة الأكثر شيوعًا بسبب سرعة تأثيره وسهولة التحكم فيه وقلة تهيجه. البروبوفول، وهو مخدر يستخدم على نطاق واسع، معروف بسرعته في العمل، ولكنه أيضًا يرتبط بعدة آثار جانبية مثل الغثيان والصداع والمشاكل القلبية الوعائية. تم تقديم سيبروفول، وهو وكيل مخدر جديد، لمعالجة محدوديات البروبوفول، بما في ذلك تقليل تكرار ردود الفعل السلبية للأدوية.(ADR)

الهدف: تقدم هذه المقالة مراجعة محدثة عن سيبروفول، مع تقييم خصائصه الهيكلية، والخصائص الدوائية، والدوائية الحركية، والفعالية السريرية كبديل للبروبوفول في التهدئة والتخدير.

الطرق: تم إجراء مراجعة للدراسات ما قبل السريرية والتجارب السريرية، بما في ذلك الدراسات من المرحلة الأولى والثانية والثالثة، لمقارنة خصائص سيبروفول المهدئة والتخديرية مع خصائص البروبوفول. كما تم تقييم التفاعلات الدوائية وملفات الأمان في بيئات سريرية متنوعة.

النتائج: أظهر سيبروفول انتقائية وارتباطًا أفضل لمستقبلات GABAA مقارنة بالبروبوفول، مما يؤدي إلى تهدئة وتخدير أكثر كفاءة عند جرعات أقل. تظهر التجارب السريرية في إجراءات مثل تنظير القولون، وتنظير المعدة، وتنظير الشعب الهوائية أن سيبروفول يوفر بدء تأثير أسرع، ومدة تهدئة مشابهة، ورضا مرضى أعلى مقارنة بالبروبوفول. كما يظهر الدواء انخفاضًا في معدل حدوث الآثار الجانبية مثل الاكتئاب القلبي التنفسي.

الخاتمة: يُعد سيبروفول بديلاً واعدًا للبروبوفول، حيث يقدم ملفًا أمنيًا أكثر أمانًا مع عدد أقل من الآثار الجانبية وتهدئة أكثر فعالية عند جرعات أقل. إن تطبيقه السريري في التهدئة أثناء تنظير الجهاز الهضمي والتخدير في العمليات الجراحية يظهر نتائج واعدة، مما يضعه كأحد الخيارات المحتملة في ممارسة التخدير .

الكلمات المفتاحية: سيبروفول، بروبوفول، تخدير، تهدئة، مستقبلGABAA ، تجارب سريرية، خصائص دوائية، دوائية حركية.