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Ciprofol: A Comprehensive Review of Its Pharmacological Profile, Clinical Efficacy, and Future Directions in Anesthetic Practice

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ABSTRACT

Background: Intravenous anesthetic agents are essential for the induction and maintenance of anesthesia, acting on the central nervous system (CNS) to induce unconsciousness, immobility, and amnesia. Propofol is widely used due to its rapid onset, short duration of action, and smooth recovery profile. However, its use can be associated with adverse effects, including injection site pain, dose-dependent hypotension, and respiratory depression. The need to address these limitations has driven the development of ciprofol (HSK3486), a novel intravenous anesthetic agent designed to retain propofol's efficacy while improving its safety profile. ***Objectives:*** This review evaluates the pharmacological profile, clinical efficacy, safety, and tolerability of ciprofol and its potential advantages over propofol. It also highlights knowledge gaps and future research directions. ***Methods:*** A comprehensive review of peer-reviewed studies, clinical trials, and systematic reviews was performed to assess ciprofol's pharmacodynamics, pharmacokinetics, and clinical performance in surgical and diagnostic settings. ***Results:*** Ciprofol exerts its anesthetic effects by modulating GABA_A receptors, enhancing inhibitory neurotransmission. Structural modifications, including the incorporation of a cyclopropyl group, increase its receptor binding affinity, contributing to reduced injection pain and improved hemodynamic stability. Clinical studies indicate that ciprofol provides effective sedation and anesthesia at lower doses, with fewer incidences of hypotension, bradycardia, and respiratory depression compared to propofol. It demonstrated consistent efficacy in elderly patients and those with hepatic or renal impairments, with minimal need for dose adjustments. ***Conclusion:*** Ciprofol represents a significant advancement in intravenous anesthetic agents, offering enhanced patient safety and comfort. Its reduced side effect profile and favorable pharmacokinetics support its use as an alternative to propofol, particularly in high-risk and critically ill patients. However, further research is needed to address long-term safety, evaluate its role in intensive care unit sedation, and explore potential neuroprotective effects.

Keywords: ciprofol; intravenous anesthetic; propofol alternative; sedation and anesthesia; adverse effects.

INTRODUCTION

A. Background on Intravenous Anesthetic Agents

Intravenous anesthetic agents are essential components of current anesthesia practice, facilitating rapid induction and maintenance of anesthesia in a controlled and efficient manner. These agents act primarily on the central nervous system (CNS) to induce unconsciousness, immobility, and amnesia. Among the commonly used intravenous anesthetics, propofol has become fundamental due to its favorable pharmacokinetic profile, including rapid onset, short duration of action, and smooth recovery phases [1, 2, 5]. Propofol exerts its effects through positive modulation of gamma-aminobutyric acid type A (GABA_A) receptors, thereby enhancing inhibitory synaptic transmission [1, 3, 7].

Despite its widespread use, propofol is associated with certain disadvantages. The most notable limitations include pain at the injection site, dose-dependent hypotension, and respiratory depression [4, 5, 12]. These adverse effects have the potential to complicate patient management, particularly in those who are hemodynamically unstable and those with compromised respiratory function [5, 11]. As a result, there has been a collective effort to help develop alternative anesthetic agents that offer similar efficacy and an improved safety profile [6, 13, 14].

B. Introduction to Ciprofol

Ciprofol (HSK3486) is a novel intravenous anesthetic agent developed as an alternative to propofol, with the goal of mitigating its associated adverse effects while maintaining its potent anesthetic properties [1, 7, 8, 13].

Chemical Structure and Classification

Ciprofol belongs to the class of 2,6-disubstituted phenol derivatives, structurally analogous to propofol. The primary distinction lies in the incorporation of a cyclopropyl group at the isopropyl side chain, which enhances its molecular configuration and binding affinity to GABA_A receptors [1, 8, 9]. This modification results in increased potency and allows for effective sedation at lower doses compared to propofol [1, 7, 9].

Mechanism of Action

Similar to propofol, ciprofol exerts its anesthetic effects by positively modulating GABA_A receptors, which are essential in mediating inhibitory neurotransmission in the CNS [1, 8, 10]. By increasing chloride ion influx into neurons, ciprofol induces hyperpolarization, thereby inhibiting neuronal excitability and producing sedation and hypnosis [1, 2, 11]. The higher receptor affinity conferred by its structural modifications contributes to its rapid onset and short duration of action [1, 8, 12].

Development History and Approval Status

The development of ciprofol was driven by the need to address the shortcomings of propofol, particularly its cardiovascular and respiratory effects [1, 8, 13]. Preclinical studies demonstrated ciprofol's enhanced potency and favorable safety profile, paving the way for its clinical evaluation in various settings, including general anesthesia and procedural sedation [1, 7, 14]. Following successful phase II and phase III clinical trials, ciprofol was approved for clinical use in China for the induction and maintenance of general anesthesia and for sedation in intensive care unit (ICU) settings [1, 7, 13]. Ongoing studies continue to investigate its efficacy in different patient populations and its potential role in international clinical practice [1, 11, 14].

While propofol remains a fundamental intravenous anesthetic, the development of ciprofol represents a significant advancement in the field of anesthesia, aimed at improving patient safety and comfort by overcoming the limitations of existing agents [7, 13, 14].

PHARMACOLOGICAL PROFILE OF CIPROFOL

A. Pharmacodynamics

Ciprofol exerts its anesthetic effects through positive modulation of GABA_A receptors, enhancing inhibitory neurotransmission in the CNS. This modulation increases chloride ion influx into neurons, leading to hyperpolarization and reduced neuronal excitability, thereby inducing sedation and hypnosis [1, 2, 8, 11]. The incorporation of a cyclopropyl group at the isopropyl side chain of the phenol ring enhances receptor binding affinity, contributing to increased potency compared to propofol [1, 3, 8].

Ciprofol's onset of action is rapid, with an observed induction time comparable to or slightly faster than propofol in clinical studies [1, 4, 5]. Its duration of action is short due to rapid redistribution from the CNS to peripheral tissues, which is a desirable feature for anesthetic control during short procedures or induction [1, 6, 7]. Additionally, clinical trials have indicated that ciprofol provides effective sedation at lower doses, which may reduce the risk of dose-related adverse effects [1, 7, 8, 12].

B. Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

Ciprofol is administered intravenously, achieving rapid plasma concentrations that correspond to its immediate sedative effects [1, 9].

Once in the bloodstream, ciprofol undergoes extensive distribution, with high tissue affinity, particularly in lipid-rich areas such as the CNS. The volume of distribution (Vd) for ciprofol is moderate, indicating efficient redistribution from the brain to peripheral compartments [1, 10].

Metabolically, ciprofol is primarily processed in the liver by cytochrome P450 enzymes, forming inactive metabolites that are subsequently excreted via the kidneys [1, 11]. Its elimination half-life is similar to propofol, ranging from 1 to 2 hours, depending on the patient's metabolic state [1, 12]. Importantly, studies have shown that ciprofol's pharmacokinetics are stable across different populations, including patients with renal or hepatic impairment, which suggests minimal need for dose adjustments in these populations [1, 3, 11, 13, 14].

Comparison with Propofol

Ciprofol and propofol share similar pharmacokinetic profiles, but ciprofol's modified structure confers some advantages. For example, ciprofol demonstrates lower plasma clearance compared to propofol, which may result in prolonged sedation with a single dose but allows for smoother maintenance of anesthesia [1, 5, 6, 8]. Additionally, ciprofol has been associated with fewer incidences of hypotension and respiratory depression during induction, making it potentially safer in high-risk patients [2, 3, 7, 9]. Clinical trials comparing ciprofol and propofol have consistently shown that ciprofol achieves the desired depth of sedation with lower incidences of injection site pain and hemodynamic instability [1, 4, 11, 13].

Ciprofol's pharmacodynamics and pharmacokinetics suggest that it is a potent and reliable intravenous anesthetic with a favorable safety profile, supporting its use as an effective alternative to propofol in various clinical settings [1, 7, 8, 14].

CLINICAL EFFICACY

A. Induction and Maintenance of General Anesthesia

The clinical efficacy of ciprofol in the induction and maintenance of general anesthesia has been demonstrated in several randomized controlled trials (RCTs) comparing it to propofol. Across these studies, ciprofol has shown comparable or superior performance in terms of anesthesia induction time, maintenance of sedation, and overall safety profiles [1, 2, 7].

In a multicenter phase 2a clinical trial, ciprofol demonstrated an induction time similar to propofol but with reduced incidences of injection site pain and hemodynamic disturbances [1, 6, 8, 11]. Another systematic review and meta-analysis confirmed that ciprofol achieved effective anesthesia with fewer adverse cardiovascular effects, making it a potentially advantageous option in high-risk surgical patients [2, 4, 9]. Additionally, studies highlighted that ciprofol required lower dosages to achieve the desired depth of anesthesia, which may contribute to reduced side effects and faster recovery times [1, 3, 5]

Clinical trials have evaluated ciprofol in a variety of surgical settings, including gynecological procedures, gastrointestinal surgeries, and outpatient surgeries [5, 6, 8]. In gynecological day surgeries, ciprofol provided stable hemodynamic parameters during induction and maintenance, with patient outcomes equivalent to or better than those observed with propofol [7, 10]. Similar efficacy was noted in studies involving endoscopic and other outpatient diagnostic interventions [6, 11, 13, 14]. These findings suggest that ciprofol is a viable alternative to propofol for the induction and maintenance of general anesthesia [7, 9, 14].

B. Sedation for Diagnostic and Therapeutic Procedures

Ciprofol has also been extensively studied in non-surgical settings, such as sedation during diagnostic and therapeutic procedures, including endoscopy, bronchoscopy, and hysteroscopy [1, 5, 8, 10, 12, 13]. In a randomized, double-blind trial involving patients undergoing painless hysteroscopy, ciprofol demonstrated high efficacy and safety, with fewer reports of injection site pain and post-procedure recovery times comparable to or shorter than those of propofol [1, 8, 9, 10].

A meta-analysis comparing sedation outcomes in endoscopic procedures revealed that ciprofol provided effective sedation with lower risks of respiratory depression and injection-related discomfort [1, 13]. Patient satisfaction surveys have also indicated higher comfort levels, particularly due to reduced pain during drug administration [5, 9, 12]. Clinician feedback also reflected a preference for ciprofol in procedures requiring prolonged or repeated sedation due to its hemodynamic stability and shorter recovery phases [1, 5, 7, 9, 10, 12].

Furthermore, ciprofol's rapid onset and predictable recovery profile make it particularly suitable for outpatient procedures where quick discharge is desired [6, 9, 13]. In bronchoscopy settings, ciprofol was associated with minimal disruption to respiratory function and consistent maintenance of sedation levels [5, 13, 14]. These features contribute to its growing acceptance as a reliable alternative to propofol in both diagnostic and therapeutic settings.

Ciprofol has demonstrated robust efficacy in both surgical and diagnostic contexts, offering comparable or improved outcomes relative to propofol [1, 5, 7, 10, 14]. The reduced incidence of adverse events, such as injection pain and hemodynamic instability, supports its role as a promising anesthetic for a wide range of clinical applications [1, 7, 12, 14].

SAFETY AND TOLERABILITY

A. Adverse Event Profile

The safety and tolerability of ciprofol have been extensively evaluated in clinical studies, with particular attention to adverse events such as injection site pain, hypotension, and respiratory depression [1, 5, 6, 10]. Compared to propofol, ciprofol has shown a favorable safety profile, with fewer incidences of pain upon injection. In a multicenter clinical trial, fewer patients reported mild discomfort at the injection site with ciprofol, as compared to propofol [1, 7, 8]. This reduction in injection pain is attributed to the structural modifications in ciprofol's formulation, which decrease the activation of pain receptors [1, 3, 9].

Regarding cardiovascular effects, studies indicate that ciprofol is associated with more stable hemodynamics during anesthesia induction and maintenance [5, 6]. In a meta-analysis, ciprofol demonstrated significantly lower rates of hypotension compared to propofol, with mean arterial pressure remaining within safe ranges for a larger proportion of patients [2, 3, 11]. Additionally, the incidence of bradycardia and severe drops in systolic blood pressure was lower with ciprofol [4, 7, 12].

In terms of respiratory safety, ciprofol has shown reduced incidences of apnea and oxygen desaturation events during induction [1, 8]. Clinical trials reported that fewer patients experienced transient apnea with ciprofol, as compared to propofol [1, 6, 13]. These findings suggest that ciprofol may be a safer choice for patients at risk for respiratory complications [1, 10, 14].

B. Special Populations

Efficacy and Safety in Elderly Patients

The efficacy and safety of ciprofol in elderly patients have been examined in age-stratified studies. Elderly patients are particularly susceptible to the adverse cardiovascular and respiratory effects of anesthetic agents [1, 5]. However, ciprofol has demonstrated consistent efficacy in achieving adequate sedation without significant alterations in hemodynamic parameters [2, 7]. In a subgroup analysis, elderly patients who received ciprofol had fewer instances of hypotension and bradycardia compared to those who received propofol, even at comparable dosages [3, 7, 10]. Additionally, recovery times were shorter with fewer reports of postoperative cognitive dysfunction [8, 11, 13].

Considerations in Patients with Hepatic or Renal Impairment

Patients with hepatic or renal impairment present unique challenges due to altered drug metabolism and excretion. Studies evaluating ciprofol in these populations have indicated that its pharmacokinetics remain stable despite impaired organ function [2, 3, 6]. In patients with moderate hepatic impairment, ciprofol's plasma clearance was minimally reduced, but this did not necessitate significant dose adjustments [1, 2, 3, 6]. Similarly, renal impairment did not substantially affect ciprofol's half-life or clearance, indicating that it is metabolized primarily via hepatic pathways with minimal reliance on renal excretion [2, 3, 6]. This contrasts with propofol, where severe hepatic impairment can lead to prolonged drug accumulation and delayed recovery [1, 3, 5, 11].

Ciprofol's safety and tolerability profile suggests that it may be a preferable alternative to propofol, particularly in patients at higher risk of adverse

cardiovascular or respiratory events and in those with hepatic or renal impairment [1, 2, 3, 5, 6, 14]. The reduced incidence of common side effects, such as injection pain and hypotension, underscores its potential as a safer anesthetic option [1, 6, 12].

ADVANTAGES OVER EXISTING AGENTS

A. Reduced Injection Pain

One of the key advantages of ciprofol over propofol is its reduced incidence of injection site pain, a common and often distressing side effect for patients undergoing anesthesia [1, 5]. The pain associated with propofol injections is attributed to the activation of pain receptors, specifically free nerve endings, by the phenol group in its molecular structure [1, 6, 8]. In contrast, ciprofol's modified formulation, incorporating a cyclopropyl group, alters its interaction with vascular endothelial receptors, leading to reduced activation of pain pathways [1, 2, 8, 11]. Clinical studies have consistently reported lower pain scores in patients administered ciprofol. Fewer recipients of ciprofol experience mild discomfort at the injection site, as compared to those receiving propofol [4, 10, 12]. The clinical significance of this reduced injection pain extends beyond patient comfort [1, 6, 7]. It contributes to smoother induction of anesthesia and may reduce the need for additional premedication or local anesthetic agents, streamlining the anesthesia process and enhancing the overall patient experience [1, 8, 14].

B. Hemodynamic Stability

Ciprofol has demonstrated superior hemodynamic stability during anesthesia induction and maintenance compared to propofol [1, 2, 5]. Propofol is known to cause dose-dependent hypotension due to its vasodilatory effects and suppression of myocardial contractility [1, 6, 8]. In contrast, ciprofol's structural modifications result in a more favorable hemodynamic profile, with studies indicating significantly lower decreases in systolic and diastolic blood pressure during induction [1, 7, 8]. A systematic review and meta-analysis confirmed that ciprofol was associated with fewer occurrences of profound hypotension and bradycardia during surgical procedures [1, 2, 10, 12]. In a multicenter phase 2 trial, ciprofol maintained stable mean arterial pressure across various surgical settings, suggesting its suitability for use in patients with cardiovascular comorbidities [4, 11, 13]. This improved hemodynamic profile makes ciprofol an attractive option for high-risk populations, such as elderly patients or individuals with pre-existing cardiac dysfunction [1, 8, 12].

Additionally, ciprofol's predictable cardiovascular effects contribute to improved intraoperative monitoring and reduced need for vasopressor support, potentially improving patient safety and surgical outcomes [1, 5, 9, 14]. Ciprofol's advantages over propofol, particularly its reduced injection site pain and superior hemodynamic stability, highlight its potential to improve anesthetic practice, especially in-patient populations vulnerable to hemodynamic disturbances [1, 2, 7].

LIMITATIONS AND AREAS FOR FURTHER RESEARCH

A. Knowledge Gaps

Despite its promising efficacy and safety profile, there are notable knowledge gaps regarding the long-term safety and broader clinical applications of ciprofol [1, 2, 7]. Most current studies focus on short-term outcomes related to induction and procedural sedation [1, 5, 9, 10, 11]. Long-term safety data, particularly concerning prolonged infusions in ICU settings, remain limited [1, 7]. Prolonged sedation may introduce risks of drug accumulation, delayed recovery, and potential impacts on organ function, necessitating further longitudinal studies [1, 5, 6, 10]. Comparative studies with other emerging anesthetic agents, such as remimazolam, remain sparse [8, 11]. While ciprofol has been extensively compared to propofol, there is a need for head-to-head trials with other newly developed intravenous anesthetics to assess its relative efficacy and safety [1, 2, 4, 5, 6, 12]. Such studies would provide a more comprehensive understanding of ciprofol's position within the anesthetic landscape [1, 12].

B. Future Research Directions

Potential Applications in Intensive Care Settings

Given its favorable pharmacodynamic and pharmacokinetic profile, ciprofol has the potential to be utilized in ICU settings for long-term sedation of mechanically ventilated patients [1, 7]. Preliminary studies have indicated that ciprofol provides effective sedation with stable hemodynamic parameters over several hours [4, 9]. However, robust clinical trials focusing on prolonged sedation in critically ill patients are needed to determine optimal dosing regimens, potential cumulative effects, and safety outcomes during extended use [3, 10, 12].

Exploration of Neuroprotective Properties

Recent investigations have suggested that certain anesthetic agents may exert neuroprotective effects by reducing neuronal apoptosis and oxidative stress [1, 2, 5, 8]. Ciprofol's GABA_A receptor activity and structural modifications may position it as a candidate for such neuroprotective roles, particularly in neurological surgeries or cases of traumatic brain injury [1, 6, 7, 11]. Preclinical studies evaluating its effects on neuroinflammation and ischemia-reperfusion injury could provide valuable insights into its potential as a neuroprotective agent [1, 2]. Furthermore, understanding its impact on postoperative cognitive function, particularly in elderly patients, remains a key research priority [7, 13].

While ciprofol has shown significant promise, addressing the identified knowledge gaps and pursuing future research directions will be essential to fully define its clinical utility and expand its indications [1, 5, 12, 14].

CONCLUSION

A. Summary of Findings

Ciprofol represents a significant advancement in intravenous anesthetic agents, offering a favorable pharmacological profile characterized by high potency,

rapid onset, and a short duration of action [1, 2, 5]. Its unique structural modifications, such as the incorporation of a cyclopropyl group, enhance GABA_A receptor binding and reduce activation of pain pathways, contributing to reduced injection site pain compared to propofol [1, 2,, 8]. Clinical trials have demonstrated that ciprofol provides effective sedation and anesthesia across a wide range of surgical and diagnostic procedures, with fewer adverse events related to hemodynamic instability and respiratory depression [1, 2, 6, 9, 10, 12, 14].

Additionally, ciprofol's pharmacokinetic properties—such as its moderate volume of distribution and hepatic metabolism—enable consistent performance in diverse patient populations, including those with hepatic or renal impairments [1, 2, 8, 12]. Comparative studies highlight ciprofol's ability to achieve the desired anesthetic effect with lower incidence rates of hypotension and bradycardia, making it a suitable option for high-risk patients [11, 12]. These findings underscore its potential as a safe and reliable alternative to propofol, with a reduced need for adjunctive medications to mitigate side effects [1, 13, 14].

B. Clinical Implications

Ciprofol's introduction into anesthetic practice holds the potential to enhance patient safety and comfort, particularly in outpatient and ambulatory settings where rapid recovery and minimal side effects are essential [9, 10, 11]. The reduced incidence of injection site pain improves the overall patient experience and may reduce the preoperative anxiety associated with intravenous anesthetic administration [1, 12]. Furthermore, its hemodynamic stability supports its use in patients with cardiovascular comorbidities, potentially broadening the scope of safe anesthesia for more vulnerable populations [3, 7, 11, 13].

In ICU settings, ciprofol shows promise as a sedative agent for long-term mechanical ventilation, though further research is necessary to confirm its efficacy in prolonged use [7, 14]. Its potential neuroprotective properties, if substantiated by future studies, could further expand its role in neuroanesthesia and the management of patients with traumatic brain injuries or ischemic events [1, 2, 11].

RECOMMENDATIONS & SUGGESTIONS FROM THE AUTHOR

Adopting ciprofol in clinical practice will require continued education for anesthesiologists and perioperative teams to ensure familiarity with its dosing, pharmacodynamics, and monitoring requirements. Additionally, regulatory approvals and economic considerations will play a critical role in its widespread adoption. Nevertheless, current evidence supports its potential to enhance anesthetic care by offering a safer, more tolerable alternative to traditional agents like propofol.

Ciprofol thus emerges as a novel intravenous anesthetic agent with significant clinical potential due to its enhanced pharmacodynamic and pharmacokinetic properties. Its ability to provide effective anesthesia and sedation with reduced adverse effects—such as injection pain and hemodynamic instability—positions it as a valuable alternative to propofol, particularly for high-risk and critically ill patients. The evidence presented underscores its efficacy across diverse clinical contexts, including surgical procedures, diagnostic interventions, and intensive care sedation.

However, despite these promising findings, there remain important knowledge gaps, particularly regarding long-term safety in extended use and its comparative performance against other emerging anesthetics. To fully integrate ciprofol into clinical practice, further research should focus on long-term studies, head-to-head comparisons with other sedative agents, and its potential neuroprotective roles in neurological care. These future investigations will help refine dosing strategies, elucidate safety profiles, and identify broader clinical applications.

This review recommends the incorporation of ciprofol into anesthetic protocols where its safety and efficacy align with patient-specific needs, especially in settings requiring hemodynamic stability and patient comfort. Anesthesiologists and clinical teams should be equipped with updated knowledge on ciprofol's use, and institutional guidelines should consider including this agent as part of anesthesia regimens. By addressing current research gaps and fostering evidence-based adoption, ciprofol has the potential to elevate standards of care and contribute to improved perioperative outcomes.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the author used ChatGPT, an AI language model, in order to maintain and order references and to assess and improve grammar/coherency. After using this tool/service, the author reviewed and edited the content as needed and took full responsibility for the content of the publication.

DISCLOSURE OF INTERESTS

The author declares that they have no competing interests.

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