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Ciprofol Dose Requirements for Successful Anesthesia Induction in Unpremedicated Children: An Up-and-Down Sequential Analysis

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ABSTRACT

This investigation sought to identify the median effective dose (ED50) and the 90% effective dose (ED90) of ciprofol that can reliably provide sedation for the induction of general anesthesia in children, refine dosing recommendations, and support clinical decision-making. Children 3–12 years old scheduled for elective procedures requiring general anesthesia and endotracheal intubation were recruited. The initial participant received 0.4 mg/kg of intravenous ciprofol. Dose adjustments for all following subjects were made using the modified Dixon up-and-down design, with each new dose based on the prior child's sedation outcome. Sedation was considered effective when both loss of eyelash reflex (LER) and facemask acceptance (AFM) occurred. ED50, ED90, and their 95% CI were calculated. Additional variables included the time until LER disappearance, induction-related vital sign alterations, and adverse reactions.

A total of 36 children completed the protocol, producing 7 success-to-failure crossover points. The ED50 and ED90 values for ciprofol were 0.618 (0.576–0.666) mg/kg and 0.708 (0.661–0.916) mg/kg, respectively. The eyelash reflex vanished at 31.04 ± 8.19 s on average. One episode of hypoxemia occurred; no injection discomfort or hypotension was noted. Ciprofol is effective for facilitating induction in pediatric patients between 3 and 12 years of age. In children without premedication, the ED50 for successful sedation is 0.618 mg/kg. A practical induction range is 0.6–0.7 mg/kg, which supports smoother mask-assisted breathing during the induction phase.

Keywords: Ciprofol, Pediatric dosing, General anesthesia, Effective dose

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Introduction

Ciprofol is a newer intravenous hypnotic agent related to propofol [1]. Unlike propofol, it is associated with reduced cardiovascular and respiratory suppression, lacks injection-site pain, accumulates minimally, and tends to cause fewer adverse reactions [2, 3]. These characteristics suggest that it may be advantageous in pediatric anesthesia. Adult induction studies have reported good performance of ciprofol at 0.4–0.5 mg/kg [4], but dose guidance for children is not yet available. Because children usually need higher induction doses of propofol than adults [5], we anticipated a similar upward shift for ciprofol. Therefore, this work applied the modified Dixon up-and-down approach to determine the ED50 and ED90 for successful pediatric induction and to offer dose-selection reference values.

Materials and Methods

Study design and patient enrollment

Approval was granted by the Medical Ethics Committee of Weifang People's Hospital, and the protocol was registered under ChiCTR2500099738. The study adhered to the Declaration of Helsinki. Pediatric patients

scheduled for elective operations under general anesthesia in April 2025 were screened. Written informed consent was obtained from legal guardians.

Inclusion criteria: (1) ASA I–II, (2) 3–12 years old, (3) scheduled for general anesthesia with endotracheal intubation.

Exclusion criteria: (1) BMI ≥28 kg/m², (2) inability to cooperate with IV induction, (3) expected difficult airway, (4) suspected drug allergy, (5) neurodevelopmental disorders, (6) use of sedatives or anesthetics within the previous 24 hours.

Interventions

The modified Dixon up-and-down method [6, 7] was used, beginning with 0.4 mg/kg ciprofol and changing doses in 0.05 mg/kg steps. Success resulted in a one-step reduction for the next patient, while failure prompted a one-step increase. The sequence ended once seven crossover events were documented. When sedation was inadequate, propofol (1–2 mg/kg) was used as rescue medication. Sedation success required simultaneous achievement of LER and AFM.

Anesthesia management

All children adhered to standard fasting requirements before surgery and did not receive any premedication. After entering the operating room, peripheral venous access was secured, and routine monitoring was initiated, including non-invasive blood pressure (NIBP), heart rate (HR), electrocardiography (ECG), pulse oximetry (SpO_2), and bispectral index (BIS). Baseline measurements were taken prior to induction.

Each child was positioned supine and given 100% oxygen through an unsealed facemask at 5 L/min for 5 minutes before induction. The first subject was administered 0.4 mg/kg ciprofol, which corresponds to the standard adult induction dose. The induction agent was injected slowly over 1 minute, followed by a 1-minute observation window for evaluating LER. Sedation was considered unsuccessful if the eyelash reflex persisted after 1 minute, prompting rescue medication. If LER disappeared within 1 minute, the child's tolerance to the facemask was assessed by elevating the mandible to the sniffing position and gently applying the mask without causing discomfort. Absence of coughing or noticeable movement indicated successful sedation; any such reactions were classified as failure. After completing all assessments, the anesthetic team administered analgesics and neuromuscular blockers as required for surgery. Dosing for the next participant was determined according to the preceding child's response.

If bradycardia or hypotension developed, atropine or ephedrine was used as appropriate. Respiratory depression (SpO_2 < 95%) was addressed through controlled mask ventilation. Once muscle relaxants were given, an endotracheal tube was placed. All anesthetic procedures were carried out by the same dedicated anesthesia team.

The study medication was prepared by an anesthesia nurse trained specifically for the protocol and aware of the dosing assignment. Before induction, the nurse calculated the ciprofol dose based on body weight, loaded the exact amount into a syringe, and sealed it in a sterile pouch. The anesthesiologist received the pouch only after the child entered the operating room. An independent investigator judged sedation effectiveness after ciprofol administration.

Primary observation: Determination of the ED50 for achieving successful sedation in pediatric anesthesia induction. Two criteria—LER and AFM—were used to assess success [8]. Sedation failure was recorded if any body movement occurred during the assessment; the absence of movement indicated success. LER was checked 10 seconds after injection and reassessed every 10 seconds for a total of 1 minute, with the time of reflex loss recorded. AFM was evaluated 1 minute after induction.

Secondary observation:

1. Assessment of hemodynamic and vital-sign changes (blood pressure, HR, SpO_2, BIS) 1 minute after induction.
2. Monitoring for adverse events during ciprofol administration, including:
    - Body movement: triggered by chin lift for mask placement or occurring spontaneously; categorized as slight or vigorous based on interference with mask positioning.
    - Respiratory depression: SpO_2 < 95%.
    - Injection pain: limb withdrawal or movement during injection.
    - Hypotension: systolic blood pressure < 70 mmHg + (2 × age).

Statistical analysis

A preset sample count was not used for this investigation; instead, recruitment continued until 7 reversals in sedation outcome were documented. The study ended immediately after the 7th crossover event, marking a change from a successful to an unsuccessful response.

To estimate the ED50 and ED90 for achieving sedation with ciprofol in pediatric anesthesia, along with their 95% confidence intervals, probit modeling was performed. The progression plot for the up-and-down dosing sequence and the modeled concentration–effect graph were produced using GraphPad Prism 5 (GraphPad Software, San Diego, CA). Additional statistical processing was completed in SPSS 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables with normal distribution are shown as mean ± standard deviation and were compared with independent-sample t-tests for baseline differences and paired t-tests for within-patient hemodynamic changes. Data not meeting normality standards are reported as median (interquartile range) [M (Q1, Q3)] and analyzed via the Wilcoxon signed-rank test. Frequency and percentage were used for categorical variables. A two-sided $\alpha = 0.05$ was adopted as the threshold for statistical significance.

Results and Discussion

A total of 36 children were included, yielding 7 crossover points, with 16 successful and 20 unsuccessful sedation outcomes. Baseline demographic information is listed in **Table 1**, and the dosing sequence based on the modified Dixon approach is shown in **Figure 1**.

Table 1. Characteristics of Patients

Characteristic	Successful Sedation Group (n = 16)	Failed Sedation Group (n = 20)	P-value
Age (years)	7.45 ± 1.89	7.13 ± 1.58	0.586
Weight (kg)	26.30 ± 9.02	29.31 ± 8.89	0.324
Height (cm)	129.13 ± 15.30	128.93 ± 12.35	0.966

Data presented as mean ± SD.

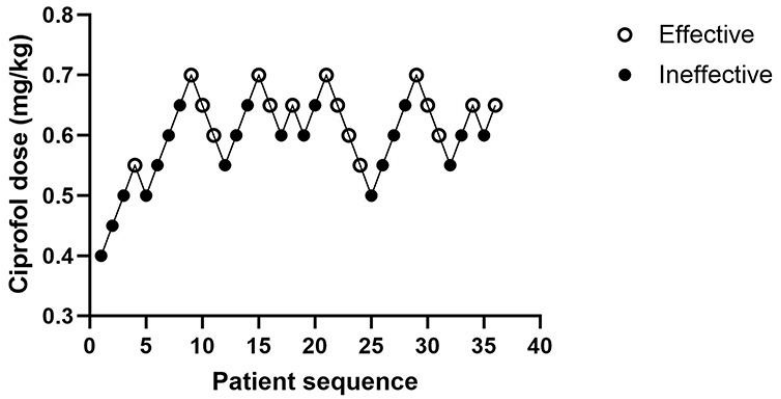

Figure 1. Up-and-down allocation pattern for ciprofol doses during pediatric anesthesia induction.

For ciprofol-assisted induction, the probit model produced ED50 = 0.618 (0.576–0.666) mg/kg and ED90 = 0.708 (0.661–0.916) mg/kg. The graphical representation of the fitted dose–response relationship appears in **Figure 2**.

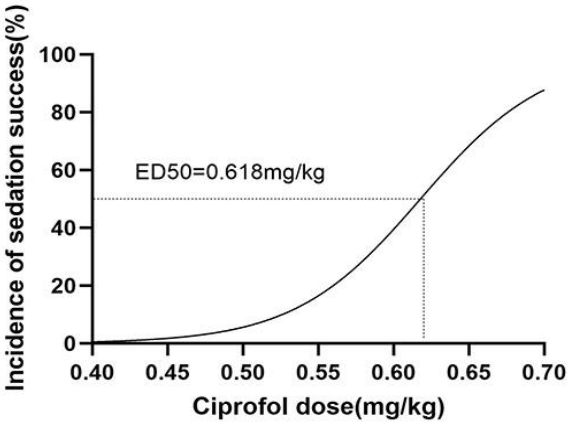

Figure 2. Fitted dose–response relationship for ciprofol used in pediatric anesthesia induction.

Vital-sign changes recorded during induction are summarized in **Table 2**. Blood pressure and BIS both showed significant reductions after induction ($P < 0.05$), whereas heart rate rose relative to baseline ($P = 0.007$).

Table 2. Vital-Sign Changes During Induction

Parameter	Baseline	1 Minute After Induction	P-value
SBP (mmHg)	110.87 ± 12.81	105.48 ± 12.53	0.005
DBP (mmHg)	69.61 ± 9.03	61.55 ± 14.41	0.001
MAP (mmHg)	80.65 ± 9.60	75.97 ± 12.40	0.020
Heart Rate (beats/min)	92.74 ± 15.14	103.13 ± 11.82	0.007
BIS	92.06 ± 4.32	42.84 ± 8.24	0.001
SpO_2 (%)	100 (99–100)	99 (99–100)	0.167

Values reported as mean ± SD or median (interquartile range).

Adverse events are detailed in **Table 3**. One case of hypoxemia occurred. No child developed injection-site discomfort or hypotension. Among the 20 instances of body movement, 19 were associated with mask ventilation, and only 1 episode occurred spontaneously without an external stimulus.

Table 3. Association Between Ciprofol Dose and Adverse Events

Ciprofol induction dose (mg/kg)	0.4	0.45	0.5	0.55	0.6	0.65	0.7
Number of patients	1	1	3	6	10	11	4
Limb movement							
– None	0	0	0	2	3	7	4
– Slight	0	0	0	1	5	4	0
– Vigorous	1	1	3	3	2	0	0
Apnea	0	0	0	0	0	0	1 (25.0%)
Injection-site pain	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	0	0

This work represents a forward-looking, dose-finding investigation conducted in children aged 3–12 years, none of whom received pre-induction premedication. Our findings indicate that the ED50 and ED90 for achieving adequate sedation with ciprofol during induction were 0.618 mg/kg and 0.708 mg/kg, respectively. Considering that ciprofol is roughly four times as potent as propofol for induction [8, 9], these doses correspond to propofol equivalents of 2.47 mg/kg and 2.83 mg/kg, which fall within the typical pediatric propofol induction range.

A variety of tools exist for evaluating sedation depth during induction, and both the eyelash reflex and the MOAA/S scale are widely used in adults [10, 11]. However, these assessment strategies do not always translate well to children. Initially, our protocol planned to use MOAA/S ≤ 1 combined with LER as the primary indicators. During early implementation, though, we observed frequent body movements after induction. Even when opioids

and neuromuscular blockers were given, movement often persisted during mask-assisted ventilation. Consequently, ciprofol doses determined using that approach would not be ideal for pediatric endotracheal intubation. For this reason, we adopted the conventional pediatric method used for propofol dose selection, relying on loss of eyelash reflex and mask acceptance as markers of adequate sedation [5, 12, 13]. This strategy helps ensure a smoother transition through the mask-ventilation stage. Hannallah additionally noted that, in clinical practice, the smoothness of the induction-to-ventilation transition is considered a central measure of successful IV induction in children, making facemask acceptance a key indicator [14].

There is currently no established dosing standard for ciprofol induction in pediatric anesthesia, and appropriate recommendations are still being clarified. Chen and colleagues reported that ciprofol is safe for both induction and maintenance in children older than 2 years, but their study did not specifically determine optimal doses in the 2–11-year age group [15]. Pei *et al*. [16] explored ciprofol at 0.4, 0.6, and 0.8 mg/kg in children aged 3–12 years to evaluate intubation conditions and found movement rates of 51%, 19.5%, and 18.3%, respectively. Although their findings differ from ours, their results also support the idea that the adult recommended induction dose of 0.4 mg/kg is inadequate for children. Opioids additionally influence ciprofol requirements: Zhang *et al*. reported that 0.5 μg/kg remifentanil significantly lowered the ciprofol ED50 needed for gastrointestinal endoscopy [17], and Wang *et al*. observed an ED50 of 1.81 mg/kg for laryngeal mask insertion when ciprofol was used without opioids [18], Because those studies involved different procedural stimuli, their dose estimates cannot be directly applied to standard pediatric anesthesia induction.

Another finding of this study is that ciprofol administration did not cause injection pain or limb withdrawal in any child. Following drug administration, 35 children lost the eyelash reflex within 1 minute, with an average disappearance time of 31.04 ± 8.19 seconds. Only one child displayed persistent spontaneous limb movement after receiving 0.6 mg/kg of ciprofol, which we suspect reflected inadequate anesthetic depth. After showing no sedation response for 1 minute, this child received 20 mg of propofol as a rescue dose. All other instances of involuntary movement occurred during mask-acceptance testing. We categorized these reactions by severity: mild movement was not clinically problematic, while more pronounced movement sometimes required assisting staff to prevent the child from slipping off the operating table. Additionally, a single episode of respiratory depression occurred within 1 minute of ciprofol administration, with oxygen saturation falling below 95%, prompting assisted ventilation.

Compared with dosage recommendations for adults, children generally need a higher amount of ciprofol to reach an adequate depth of anesthesia. At the same time, clinical experience indicates marked variability among pediatric patients in how they respond to the drug, making it necessary to use monitoring tools for anesthetic depth and to tailor dosing on an individual basis. Using the pediatric ED50 and ED90 values obtained in this investigation, we propose an induction dose range of 0.6–0.7 mg/kg for pediatric patients.

This work has several constraints. To begin with, the study population was limited to relatively healthy children classified as ASA I–II who were scheduled for elective procedures, which reduces generalizability to higher-risk groups. Moreover, although the enrolled participants were 3–12 years old—a fairly broad developmental span—the study did not perform age-specific subgroup evaluations.

Conclusion

Ciprofol is effective for the induction of anesthesia in children aged 3–12 years. Without any premedication, the median effective dose (ED50) needed to achieve successful sedation during induction was 0.618 mg/kg. For routine induction in pediatric patients within this age bracket, a dosage of 0.6–0.7 mg/kg is recommended to promote a stable transition during mask-assisted ventilation.

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Conflict of Interest: None

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Ethics Statement: None

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