

A case report of ciprofol overdose during anesthesia/analgesia and literature review: clinical presentation, blood pressure, and management

Journal of International Medical Research

2022, Vol. 50(11) 1–7

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DOI: 10.1177/03000605221132466

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Abstract

Ciprofol is a novel intravenous anesthetic agent and a highly selective gamma-aminobutyric acid-A receptor agonist, similar to propofol. This is the first report about ciprofol overdose occurring during the maintenance phase of anesthesia for a surgical intervention. The accidental administration of an excessive ciprofol dose to a 37-year-old woman admitted to our hospital for laparoscopic myomectomy occurred during the first 3 minutes of maintenance anesthesia, in which the administered dose was 3.67 mg/kg instead of 0.06 mg/kg. The patient's bispectral index (BIS) decreased to 0 after 6 minutes and returned to 26 after 23 minutes, after which the surgery was restarted and successfully completed with the planned ciprofol maintenance anesthesia dose. During the 23 minutes after ciprofol overdose, the patient's vital signs were stable with the lowest mean arterial pressure being 69.3 mmHg. The patient regained consciousness quickly and recovered well after myomectomy. The patient's BIS decreased progressively, whereas her blood pressure, heart rate, and oxygen saturation did not change significantly. In the present case of ciprofol overdose, the observed stable blood pressure protected against organ injury during laparoscopic myomectomy.

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Keywords

Propofol, ciprofol, anesthesia, overdose, bispectral index, myomectomy

Date received: 12 May 2022; accepted: 23 September 2022

Introduction

Ciprofol is a 2, 6-disubstituted phenol derivative¹ that was developed for procedural sedation and general anesthesia. It is a gamma-aminobutyric acid-A (GABA_A) receptor agonist,^{2,3} and previous *in vitro* studies recorded EC₅₀ values of ciprofol and propofol for GABA_A receptor-mediated current enhancements of 1.1×10^{-6} and 5.3×10^{-6} M, respectively, suggesting that ciprofol is a more potent sedative than propofol. Previous phase 1 trials revealed that single intravenous ciprofol injections at doses of 0.4 and 0.5 mg/kg had comparable clinical effects as 2.5 mg/kg propofol, and the former drug was well tolerated up to 0.9 mg/kg.⁴ In 12 completed phase 1 to 3 clinical studies, it was confirmed that ciprofol can be used for the induction and maintenance of anesthesia in adults undergoing surgery, including gastrointestinal endoscopy,⁵ and for the sedation of patients in the intensive care unit (ICU).⁶ Ciprofol has been approved in China by the National Medical Products Administration, but it has not yet been authorized by the US Food and Drug Administration. This report describes a case of ciprofol overdose under erroneous operations that did not cause clinically significant injury to the patient, and the findings support the good safety of ciprofol.

Case presentation

A 37-year-old woman with American Society of Anesthesiologists grade I uterine fibroids was scheduled to undergo laparoscopic myomectomy as a participant in

a phase 3 trial for ciprofol use as an anesthetic for surgical interventions. The present intervention was her first instance of anesthesia and surgery. The patient never smoked, and she had a history of chronic gastritis, thyroid nodule, vitamin D deficiency, and Hashimoto's thyroiditis but not hypertension, hypotension, allergy, or alcohol consumption. At baseline, the airway assessment (modified Mallampati score) was Class I.

After she entered the operating room, her vital signs were monitored, the peripheral veins of the upper extremity were opened, and catheterization of the lower left radial artery was performed under ultrasound guidance. The basic vital signs of the patient were as follows: blood pressure (BP), 119/77 mmHg; heart rate (HR), 67 beats/minute; respiration rate (RR), 15 breaths/minute; and bispectral index (BIS), 95. Induction anesthesia was initiated with 2 mg of midazolam, 15.25 µg of sufentanil, 0.4 mg/kg ciprofol, and 30 mg of rocuronium bromide, which were successively given as bolus injections according to the protocol requirements. Mechanical ventilation was immediately started following successful endotracheal intubation.

Following the induction of anesthesia, the patient's vital signs were as follows: BP, 127/85 mmHg; HR, 75 beats/minute; RR, 17 breaths/minute; and BIS, 41. Continuous infusion of 0.2 µg/kg/minute remifentanyl and 1.19 mg/kg/hour ciprofol as maintenance medication was initiated. After 1 minute, the patient's vital signs were as follows: BP, 114/71 mmHg; HR, 74 beats/minute; RR, 13 breaths/minute;

and BIS, 39. After 2 minutes, her BP, HR, RR, and BIS were 114/72 mmHg, 69 beats/minute, 12 breaths/minute, and 27, respectively. After her vital signs deteriorated (BP, 105/52 mmHg; HR, 70 beats/minute; RR, 12 breaths/minute; and BIS, 12), we decided to decrease the ciprofol dose. During this adjustment, we found that the infusion pump was incorrectly set (the initial rate of the infusion was set at 1.19 mg/kg/minute instead of 1.19 mg/kg/hour) and the infusion was stopped immediately. The infusion speed was incorrectly set for 3.1 minutes, leading to a total dose of 3.67 mg/kg instead of 0.06 mg/kg. Within the next 5 minutes, the patient's BIS dropped to 0 and remained below 0 for the next 2 minutes, after which the value began to rise gradually to 26 within the subsequent 16 minutes. During this period, the patient's HR, BP and blood oxygen saturation fluctuated within the normal ranges with the lowest mean arterial pressure (MAP) being 69.3 mmHg (Figure 1). Because the patient's vital signs other than BIS were stable during the 23-minute observation period, the multilateral

communication consultation team decided to continue surgery as planned. Maintenance anesthesia was again initiated with continuous infusions of 0.2 µg/kg/minute remifentanyl and 1.19 mg/kg/hour ciprofol when the patient's vital signs were as follows: BP, 103/64 mmHg; HR, 53 beats/minute; RR, 12 breaths/minute; and BIS, 26. Surgery was resumed 1 minute later. During the operation, the dosage of ciprofol was adjusted over time according to changes in the patient's vital signs. To reduce bleeding during the operation, 6 units of pituitrin were intravenously delivered 12 minutes after the skin incision. At 33 minutes after the skin incision, the patient's HR decreased for 4 minutes, with the lowest value being 47 beats/minute. Therefore, 0.4 mg of atropine sulfate was injected. Until the subsequent skin suture after 1 hour, the patient's vital signs were stable, and 14 minutes after the skin was sutured, the patient regained consciousness with immediate vital signs as follows: BP, 128/88 mmHg; HR, 68 beats/minute; RR, 12 breaths/minute; BIS, 88; and Modified Observer's Assessment of Awareness/

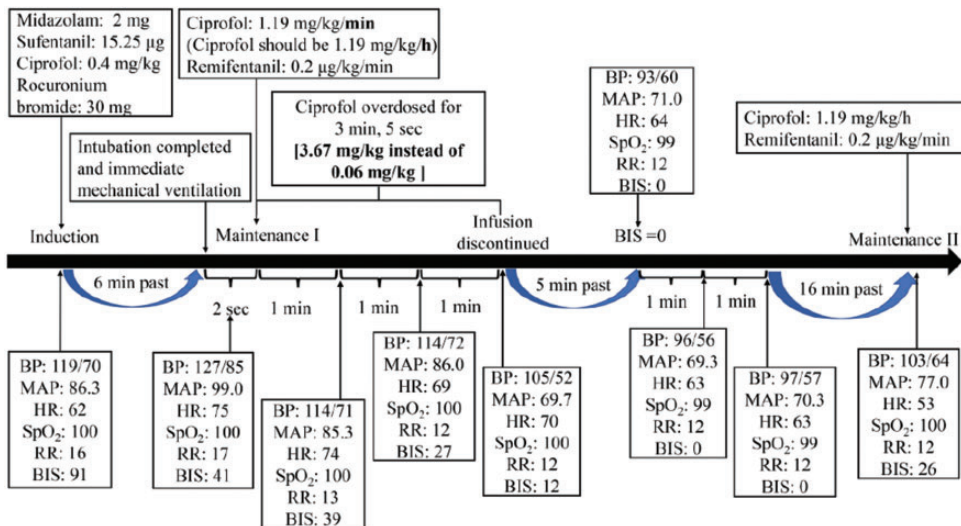


Figure 1. Vital signs before, during, and after the ciprofol overdose.

Sedation Scale, 5 points. Consequently, the endotracheal tube was removed. Ten minutes later, the modified Aldrete score was 10 points, and after 1 hour, the patient was returned safely to the ward. When the patient left the operation room, her vital signs were as follows: BP, 123/76 mmHg; HR, 87 beats/minute; RR, 13 breaths/minute; and BIS, 88. A non-blinded researcher went to the ward approximately 1 hour later to check the patient's postoperative recovery. The patient was conscious; she did not complain of dizziness, nausea, vomiting, limb movement disorder, or other discomforts; and her vital signs were stable. On a subsequent examination, the patient was evaluated by a multidisciplinary team including physicians in neurology, general surgery, anesthesiology, and psychosomatic medicine, who all agreed that the patient's condition had normalized without brain or other organ dysfunction.

On the next day, the patient was conscious, her vital signs were stable, and she had no complaints of special discomfort. She was subsequently discharged. The follow-up examination revealed normal findings on electrocardiogram, and apart from abnormal albumin and total protein concentrations in the blood biochemical report, other blood routine indices were normal. The patient approved publication of her case history.

The reporting of this study conforms to CARE guidelines.⁷

Discussion

Intraoperative hypotension (IH) is a common side effect during non-cardiac surgical interventions that results in increased risks of 30-day postoperative major adverse cardiac or cerebrovascular events.⁸ A previous study reported that even short periods with intraoperative MAP < 55 mmHg were associated with acute kidney and myocardial injuries.⁹ To avoid organ hypoperfusion

during anesthesia, a previous study introduced individualized blood pressure management in which high-risk patients received treatments for maintaining systolic blood pressure (SBP) within 10% of their resting reference SBP *versus* standard-of-care therapy for patients with SBP < 80 mmHg or decreases of >40% of the reference SBP during major surgery. Consequently, individualized treatment led to significantly lower rates of postoperative renal dysfunction and altered consciousness compared with the standard treatment.¹⁰ However, another study concluded that to avoid myocardial and kidney injury, anesthetic management of blood pressure can be based on intraoperative MAP without considering the preoperative pressure.¹¹ Propofol-related IH usually occurs after the induction of anesthesia and before the start of surgery, whereas the incidence of IH during propofol-based anesthesia has been reported to be 26%.^{12,13} Another study found that propofol was commonly administered at 1.8 to 2.2 mg/kg above the recommended doses for the induction of anesthesia, and these increased doses were associated with increased risks of post-induction hypotension, especially in elderly patients.¹⁴ In the present case, the patient received a ciprofol overdose of 60 times the planned dose over a period of 3 minutes, but the total amount administered was approximately 4.08-fold higher than the highest ciprofol dose (0.9 mg/kg), which was given as a bolus injection in previous phase 1 trials.⁴ After ciprofol overdose, the patient's blood pressure dropped from 120/70 mmHg to 105/55 mmHg at the end of the overdose infusion and stabilized at 95/60 mmHg during the next few minutes before returning to 104/67 mmHg when the maintenance infusion was restarted with the proper ciprofol dose. The heart rate during this period was ranged from 55 to 70 beats/minute. The patient's MAP decreased to as low as 69.3 mmHg at

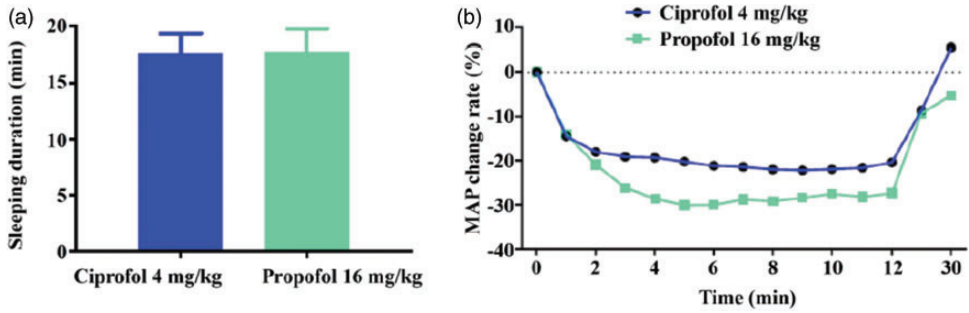


Figure 2. Results in a rat model comparing ciprofol and propofol overdoses. (a) Sleeping duration of the rats after injections and (b) MAP change rates in the rat groups after drug injections. In male Sprague–Dawley rats weighing 250 to 300 g, a pressure catheter was implanted 0.5 cm in the centripetal direction of the iliac artery branch for telemetry transmission of hemodynamic parameters. The treatments comprised injections of 4 mg/kg ciprofol ($n=4$) and 16 mg/kg propofol ($n=3$) in the tail veins. MAP, mean arterial pressure.

9.5 minutes after the overdose injection was started, and MAP was 77 mmHg at the second maintenance anesthesia initiation. This value was far lower than that in a previous case report, which documented a 5-fold overdose of propofol in a 38-day-old infant decreased blood pressure to 60/20 mmHg (MAP \approx 35 mmHg) before recovering 15 minutes later.¹⁵

The present data indicated that ciprofol overdose appears to have weaker effects on hemodynamics than an overdose of propofol. To further examine the probability of this assumption, an anesthetic overdose experiment was performed in a recent animal study in which the effects of 4 mg/kg ciprofol were compared with a comparable overdose of 16 mg/kg propofol in a rat model.¹⁶ The results illustrated that despite the same effects on sleep duration (Figure 2a) ciprofol overdose led to essentially fewer MAP reductions than a comparable propofol overdose (Figure 2b).

One limitation of the present study is that a single patient's data cannot be extrapolated to a wide range of patients because varying factors such as age and comorbidities are not included in the results of a single case.

In summary, ciprofol overdose did not lead to serious perioperative complications in our patient. Although BIS of the patient was 0 within 5 to 7 minutes, the patient's orientation and consciousness recovered well after the operation as evaluated by an MDT, and these findings indicate that excessive infusion did not have serious consequences on the patient's brain function.

Author's contributions

Conceptualization: MY; Data curation: LY, AW, SM, GJ, MY and JZ; Investigation: MY; Supervision: MY; Validation: LY, AW, SM, GJ, MY and JZ; Writing – original draft: LY, AW, SM, GJ and MY; Writing – review & editing: MY and JZ.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Ethics statement


The study was approved by the Ethical Committee of Sichuan Provincial People's

Hospital (Approval No. 2020-38-1) and written informed consent for treatment and publication of the case report was obtained from the patient.

Funding

Funding information is not available.

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