# Prolonged Apnea After Small Single Dose of Intravenous Tramadol

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*We report an unusual case of respiratory depression and prolonged apnea after a single, 50-mg intravenous dose of tramadol. Shortly after an uneventful surgery and anesthesia, the patient was administered intravenous tramadol. Soon after the tramadol injection, the patient became apneic, did not respond to verbal command, and started exhibiting oxygen desaturation. He was quickly administered 100% oxygen and positive pressure ventilation via a Bain circuit, and it took 45 minutes for the spontaneous respiration to return to regular.*

*The respiratory depression could be due to increased amount of (+)enantiomer in that ampoule of tramadol. Physiological parameters affecting the metabolism of either enantiomer of tramadol or perioperative drugs need to be evaluated, as do physiological changes affecting the activity or metabolism of (+)enantiomer. This case report demonstrates that even a small single dose of tramadol administered intravenously in the immediate postoperative period after general anesthesia may manifest as sudden and prolonged apnea.*

***Keywords:*** Anesthesia, apnea, enantiomer, single dose, tramadol.

The reputation of tramadol, as an analgesic lacking respiratory depression, has contributed to its increased clinical use in intraoperative and postoperative periods.[1] Tramadol has been safely used even in patients with obstructive sleep apnea without any sedative effect postoperatively.[2,3] Respiratory depression with tramadol has been reported in patients with impaired renal functions and *CYP2D6* gene duplication.[4,5] Here we report an unusual case of respiratory depression and prolonged apnea after a small, single intravenous dose of tramadol.

## Case Summary

A 20-year-old, 45-kg man presented to us with chief complaints of bilateral nasal obstruction and nasal bleeding for the last 2 years. He gave a history of occasional frontal headache and excessive snoring during sleep for the same duration. However, features suggestive of obstructive sleep apnea were absent. The patient reported intake of no medications. Findings of routine laboratory investigations, including serum urea nitrogen (25 mg/dL) and serum creatinine (0.9 mg/dL), were normal. Systemic examination revealed no abnormality. Local examination revealed a soft palate bulge with a soft-tissue mass filling the left nasal cavity. Indirect laryngoscopy showed normal and mobile cords. Biopsy revealed a benign nerve sheath tumor, for which a left lateral rhinotomy for excision of the mass was planned, to be performed under general anesthesia. No sedative premedication was advised.

We used a standard anesthesia technique, with fentanyl (2 mg/kg), propofol (2 µg/kg), vecuronium (0.1 mg/kg), and intermittent positive pressure ventilation (IPPV) with 100% oxygen for orotracheal intubation. Isoflurane (1 to 1.2 minimum alveolar concentration, or MAC) in oxygen, nitrous oxide (50:50), along with boluses of fentanyl (0.5 µg/kg each; total administered, 90 µg at induction and 40 µg during maintenance) and vecuronium were used for maintenance of anesthesia. The surgery lasted 3 hours, and intraoperative blood loss was approximately 800 mL. The last dose of fentanyl was administered 1 hour before completion of surgery. At the end of the surgery, the residual neuromuscular blockade was reversed with 2.5 mg of neostigmine and 0.4 mg of glycopyrrolate. In view of extensive nasal, palatine, and pharyngeal dissection and a concern for posterior pharyngeal bleeding, we planned to keep the endotracheal tube in situ overnight.

After we ensured a full recovery from neuromuscular blockade and regular breathing, the patient was transferred to the postanesthesia care unit (PACU) and connected to an oxygen supply (5 to 6 L/min) via a T-piece system. Postoperatively he was conscious, oriented, and maintaining vital signs (heart rate, 86/min; blood pressure, 130/70 mm Hg) and normal oxygen saturation levels as measured by pulse oximetry ($Spo_2$, 99%). In the PACU, 20 minutes later, the patient complained of pain

(5 on a visual analog scale, or VAS). Thus, tramadol (50 mg) was slowly administered intravenously.

Soon after the tramadol injection, the patient became apneic, did not respond to verbal command, and started exhibiting oxygen desaturation ($Spo_2$, 89% to 90%). He was quickly administered 100% oxygen and positive pressure ventilation via a Bain circuit. It took 45 minutes for the spontaneous respiration to return to regular. He was kept under observation overnight and extubated the next morning after we checked for evidence of no posterior pharyngeal bleeding. He subsequently made an uneventful recovery.

## Discussion

Tramadol is a centrally acting synthetic 4-phenylpiperidine analogue of codeine, which is an analgesic agent acting as both a weak opioid agonist and an inhibitor of monoamine neurotransmitter reuptake for the treatment of moderate to severe pain. The efficacy of tramadol has been confirmed in postoperative, neuropathic, and osteoarthritic pain. Unlike other opioids, it is well tolerated and has no clinically relevant effects on cardiovascular parameters. The marketed product is a racemate mixture containing 50% of a (+)enantiomer and 50% of a (–)enantiomer. The analgesic effect of tramadol is mediated through 2 distinct but complimentary mechanisms of action. It acts as an opioid agonist with selectivity for the μ-opioid receptor and binds weakly to the κ- and δ-opioid receptor. The (+) and (–)enantiomers differentially contribute to the analgesic effect of racemic tramadol, which is the clinically used form of the drug. The (+)enantiomer has a greater affinity for the μ-receptor and is a more effective inhibitor of serotonin reuptake, whereas the (–)enantiomer is a more effective inhibitor of norepinephrine reuptake and increases norepinephrine release by autoreceptor activation.[6] In a pilot study, Grond et al,[7] using patient-controlled analgesia with tramadol, concluded that the (+)enantiomer and racemate of tramadol were more potent analgesics than (–)enantiomer, whereas the incidence of adverse events was higher in patients receiving (+)enantiomer than with racemate.

The analgesic and antinociceptive effects of tramadol are only partially antagonized by the opioid antagonist naloxone, which suggests that nonopioid mechanisms are also involved.[8] Plasma concentrations of tramadol, its enantiomers and *O*-desmethyltramadol have been found to show considerable interindividual variations.[6]

The polymorphic cytochrome P450 2D6 (*CYP2D6*) appears to be a major enzyme involved in the metabolism of tramadol enantiomers. Tramadol undergoes biotransformation in the liver and is excreted via the kidneys. Of 11 known metabolites, only the *O*-desmethyltramadol is pharmacologically active and has a greater affinity at the μ-receptor than its parent compound.[6,9] It also has significant opiate side effects (100 times more than those of tramadol isomers by themselves).[10]

To our knowledge, no case has been reported where such a small single dose of tramadol is associated with prolonged apnea. Our patient did not have any history of renal dysfunction, as results of kidney function tests were normal. Although we could not obtain an evaluation for the *CYP2D6* gene, we think that the respiratory depression could be due to an increased amount of (+)enantiomer in that ampoule of tramadol. Physiological parameters affecting the metabolism of either of the enantiomers of tramadol or perioperative drugs, and physiological changes affecting the activity or metabolism of (+)enantiomer, need to be evaluated. Through this case report, we want to emphasize that even a small single dose of tramadol administered intravenously in the immediate postoperative period after general anesthesia may manifest as sudden and prolonged apnea.

Hence, we recommend that tramadol should be used only in a monitored environment and that even a small single intravenous dose may not be safe. Caution should be exercised in this regard, especially where adequate facilities for postoperative monitoring are not fully developed.

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