

Remifentanyl apnea: Case report and review of the literature

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Abstract

Remifentanyl is an opioid analgesic frequently used in intensive care patients because of its rapid onset of action, potency, and ultra-short duration. If an excessive dose is given, it leads to rapid, short lasting, potentially life-threatening side effects such as apnea, bradycardia, hypotension, and rigidity, following rapid peak serum levels. We report a 36-year-old woman developing apnea with bradycardia and hypotension, following an infusion in the central venous catheter lumen that had been used for remifentanyl till tracheal extubation. The patient was immediately ventilated with bag-valve-mask and improved within 8 minutes. She became fully awake, heart rate and blood pressure returned to normal, and oxygen saturation improved to 100%. Acute care physicians, intensivists, anesthesiologists, and critical care nurses should be aware of this clinical problem in order prevent it as much as possible and to initiate immediate resuscitative measures.

Key words: Apnea, bolus dose, bradycardia, hypotension, remifentanyl

Introduction

Intensive care patients often require continuous analgesic and sedative agents. Remifentanyl is a commonly used analgesic in both intensive care and anesthesia practices. It is a potent opioid analgesic with ultra-short duration of action, extremely rapid peak effect, and an equally consistent and rapid elimination with complete cessation of effect within a maximum of 10 minutes. In clinical practice, it behaves as an “on and off switch.”^[1] These properties make remifentanyl an analgesic of choice in intensive care patients. An excessive bolus dose however can cause rapid onset of potentially life-threatening side effects, such as bradycardia, hypotension, muscular rigidity, and apnea.^[1]

We report a case of an inadvertent remifentanyl bolus which induced sudden bradycardia, hypotension, and apnea. It was

immediately detected and successfully managed in our surgical intensive care unit (SICU).

Case Report

A 36-year-old woman was admitted to SICU after resection of a hepatic mass. She was intubated, ventilated, and sedated with propofol and remifentanyl infusion provided analgesia. On the second postoperative day, the abdominal packs were removed and hemostasis was achieved. She remained hemodynamically stable, was weaned from the ventilator, and extubated on day 4.

Propofol and remifentanyl infusions were stopped 1 hour and 15 minutes before the extubation, respectively. After tracheal extubation, the patient was fully awake, breathing spontaneously, respiratory rate was 20-24 breaths per minute, oxygen saturation was 100%, and she was hemodynamically stable. Thirty minutes after extubation, the lumen of the central venous catheter, used for the remifentanyl infusion up to 15 minutes prior to extubation, was used to infuse a plasma protein fraction bag at a rate 125 ml/hour.

Within 2-3 minutes, the heart rate of the patient decreased to 48 beats per minute, oxygen saturation dropped to 60%, she stopped breathing, and systolic blood pressure decreased to 86 mm of Hg [Figure 1]. She was immediately ventilated with bag-valve-mask. Atropine was given, and within 3 minutes her heart rate increased to 60 beats per minute and her blood

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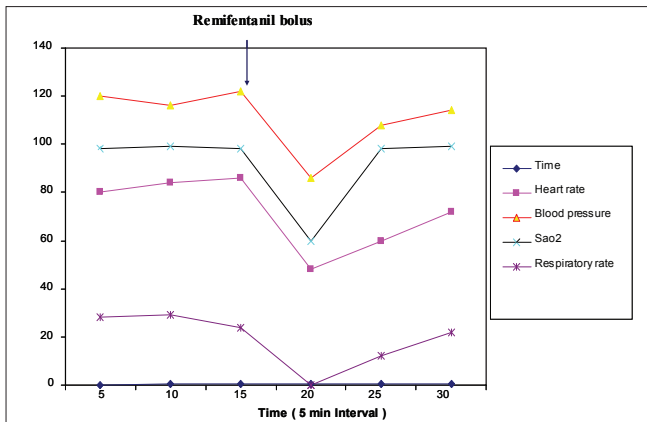


Figure 1: Remifentanyl bolus dose and its effects

pressure improved to 108 mm of Hg. The patient started to breathe and was fully awake after 8 minutes. Concurrently, her heart rate and blood pressure improved (72-74 beats per minute and 112-120 mm of Hg, respectively) oxygen saturation reached 100% with a respiratory rate of 22-24 breaths per minute (Oxygen supplementation 5 liters per minute was given by nasal canula). The patient remained awake, hemodynamically stable, and breathed spontaneously. She was transferred to the surgical ward on day 6 and later discharged home.

Discussion

Remifentanyl is an ultra-short acting opioid analgesic which acts on mu-receptors; it has a rapid onset of action (1.3 minutes). This combined with an ultra-short duration of action and rapid elimination (3 minutes) makes remifentanyl an analgesic medication of choice in ICUs.^[2]

If an excessive remifentanyl bolus dose is injected, it leads to potentially life-threatening adverse effects such as bradycardia, hypotension, muscular rigidity, and apnea.^[1] The use of remifentanyl for patient-controlled analgesia (PCA), in which the bolus dose of remifentanyl range between 0.25 and 1 $\mu\text{g}/\text{kg}$ has been described.^[3] Even with this dose, 20% of the patients suffer oxygen desaturation. Ten patients were evaluated during remifentanyl-PCA following cardiac surgery. Remifentanyl-PCA was provided with a bolus facility of 50 μg administered over 5 minutes, followed by a 5-min lockout in combination with a background infusion. This technique seemed to be safe and effective in this group of patients.^[4]

Bowdle *et al.* studied the effects of remifentanyl in the immediate postoperative period; 29% patients developed respiratory adverse events. Interestingly, apnea occurred in 8.7% patients and 83% of them received a bolus dose of remifentanyl.^[5] In this study, remifentanyl was connected by piggy bag into

the main standard intravenous infusion line. Depending on the type of tubing used and the site of connection, the dead space of the main intravenous tubing between the port where remifentanyl is inserted into the main intravenous infusion line and the patient's vein can vary from 1 to 5 ml. In these conditions, a change in the flow rate of the intravenous fluid will have a clear impact on the delivery of remifentanyl. If the flow in the main intravenous tubing is suddenly increased, the amount of remifentanyl contained in the dead space will be flushed abruptly into the patient's circulation, leading to a bolus effect of remifentanyl mainly bradycardia, hypotension, apnea, and rigidity.^[5]

In our patient, remifentanyl was used in a standard solution of 400 $\mu\text{g}/\text{ml}$. As the patient was on higher dose (0.4 $\text{mcg}/\text{kg}/\text{minute}$) of remifentanyl, higher concentration of drug infusion was used. 1-2 ml may have remained in the tubing and bivalve connection must have been flushed when the same port and connection were used to infuse the plasma protein fraction with higher rate (125 ml/hour). The bolus dose of the remifentanyl flushed must have been around 400-800 μg . This is sufficient to cause the potentially life-threatening adverse effects encountered in this patient. Bowdle *et al.* have also reported a case of one patient becoming unconscious, cyanosed, and bradycardic after an intravenous line was flushed; the same line was used for remifentanyl infusion.^[5] To avoid such serious preventable clinical problems, Hug has suggested ventilation with a bag-valve-mask and following recommendations.^[6]

1. Avoid intravenous bolus and flushing of the line which was used for remifentanyl infusion.
2. Treat and/or prevent bradycardia and hypotension with anti-cholinergic medications.
3. If apnea and rigidity occur with excessive bolus of remifentanyl, it will be difficult to give positive pressure ventilation. In this situation, a short-acting muscle relaxant can be used and the patient ventilated until the effects of the bolus dose wear off.

To prevent similar incidents in our ICU in future, we started to use a more diluted remifentanyl infusion, given through a dedicated cannula or connecting remifentanyl infusion closer to the patient using a three way, and started to remove the infusion lines used, to place the remifentanyl on hold for preparing the patient for extubation. It is essential to be aware of these rapidly occurring, potentially life-threatening effects of excessive bolus doses of remifentanyl. Acute care physicians, intensivists, anesthesiologists, and critical care nurses must be aware of this to ensure proper management.

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