Diffuse alveolar hemorrhage following sugammadex and remifentanil administration
A case report

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Abstract

Rationale: Diffuse alveolar hemorrhage (DAH) is a rare life-threatening condition that accompanies general anesthesia. Negative-pressure pulmonary edema (NPPE) is a rare cause of DAH.

Patient concerns: A 25-year-old male patient developed hemoptysis following remifentanil administration by bolus injection with sugammadex at the emergence from general anesthesia.

Diagnosis: Chest x-ray and computed tomography showed DAH.

Interventions: Conservative care was provided with 4L of oxygen via nasal prong, 20 mg of Lasix and 2500 mg of tranexamic acid.

Outcomes: The patient was discharged uneventfully.

Lessons: Muscle rigidity by remifentanil and the dissociated reversal of neuromuscular blockade by sugammadex was suspected as the cause of NPPE-related DAH. Therefore, the possibility NPPE-related DAH should be considered when using a bolus of remifentanil and sugammadex during emergence from general anesthesia.

Abbreviations: CRP = C-reactive protein, DAH = diffuse alveolar hemorrhage, ECG = electrocardiogram, FiO₂ = fraction of inspired oxygen, Hb = hemoglobin, NPPE = negative-pressure pulmonary edema, PACU = Post-anesthesia Care Unit, PT = prothrombin time, SPO₂ = saturation of pulse oximetry, WBC = white blood cell count.

Keywords: diffuse alveolar hemorrhage, negative pressure pulmonary edema, remifentanil, sugammadex

1. Introduction

Diffuse alveolar hemorrhage (DAH) is an infrequent but life-threatening complication related to anesthesia. Negative-pressure pulmonary edema (NPPE) is a rare cause of DAH. NPPE is associated with upper airway obstruction.[2] Upper airway obstruction caused by glottis closure and laryngospasm leads to marked inspiratory efforts, which generate strongly negative intrathoracic pressure causing pulmonary edema[2,3] and, rarely, hemoptysis.[4]

Bolus dosing of remifentanil may cause unwanted effects such as muscle rigidity, which causes sudden adduction of vocal cords or supraglottic obstruction by soft tissue, resulting in upper airway obstruction. Sugammadex induces the dissociated recovery from the effects of neuromuscular blockade between the upper airway smooth muscle and respiratory muscles such as the diaphragm, which show a low response to muscle relaxants. As a result, rapid rise in effective respiratory muscle strength during upper airway obstruction induces negative intrathoracic pressure, resulting in NPPE-related DAH.

We experienced a case of NPPE-related DAH following a bolus injection of remifentanil and reversal of rocuronium-induced neuromuscular blockade by sugammadex during emergence from general anesthesia. In the present case, remifentanil-induced muscle rigidity and the dissociated reversal by sugammadex is suspected as the cause of NPPE-related DAH.

2. Case description

This case was approved by the institutional review board of Uijeongbu St. Mary's Hospital of Catholic University of Korea. The patient provided informed consent for the publication of his clinical and imaging data. A 25-year-old male patient (173 cm, 81 kg, BMI 27.0) was scheduled to undergo bilateral orchiopexy for testicular torsion. His medical history and preoperative physical examination were unremarkable. The patient’s vital signs and laboratory findings were as follows: blood pressure, 143/64 mmHg; heart rate 94 beats/min; saturation of pulse oximetry (SpO₂) 100%; white blood cell count (WBC) 12.21 \times 10^9/L; hemoglobin (Hb) 15.1 g/dL; platelet count 246 \times 10^9/L; C-reactive protein (CRP), 0.06 mg/dL; prothrombin time (PT) (INR) 1.25 (0.9–1.22); PT, 14.0 seconds (9.9–13.5 s); and
activated partial thromboplastin time (aPTT) test, 19.3 seconds (21.0–38.0 s). A preoperative chest x-ray was within the normal range. Anesthesia was induced with lidocaine (40 mg), propofol (2 mg/kg, total 160 mg), and remifentanil (0.2 mcg/kg/min). After confirming loss of consciousness, 50 mg rocuronium (0.625 mg/kg) was administered and endotracheal intubation was carried out without any complications. During the operation, anesthesia was maintained with 6.0 vol% of desflurane and continuous infusion of remifentanil (0.06 mcg/kg/min). During the procedure, the bispectral index (BIS) scale was maintained between 30 and 40, and end-tidal CO₂ was 32 mmHg. The patient showed stable blood pressure and oxygen saturation was maintained between 99 and 100% while 2L of air and 1L of oxygen (FiO₂ 0.4) were administered. The duration of surgery was about 110 minutes and 900 mL of crystalloid was administered. After surgery, sugammadex 200 mg (2.5 mg/kg) was administered. A bolus dose of remifentanil 30 mcg (0.37 mcg/kg) was administered to prevent cough, agitation, and hemodynamic disturbances associated with anesthetic emergence during extubation.

The patient began spontaneous ventilation and subsequently the trachea was extubated. Immediately after extubation, the patient failed to breathe well, and the anesthesiologist tried manual bag ventilation using oral airway and jaw tilting. Mask ventilation was not effective and assuming that the cause of difficult ventilation was muscle rigidity induced by remifentanil, we administered naloxone 0.2 mg (2.5 mcg/kg). After injection of naloxone, the patient performed a sudden deep breath. A few minutes later, the patient coughed and spat out pink sputum. Hemoptysis was observed and wheezing was heard during chest auscultation while electrocardiogram (ECG) revealed normal sinus. The vital signs were as follows: blood pressure, 152/72 mmHg; heart rate, 72 beats per minute; respiratory rate, 16/min; and SpO₂, 100% with 100% oxygen. On arrival at the PACU, the SpO₂ level was 80%. The SpO₂ was elevated to only 91% despite providing 5L of oxygen via facial mask. Subsequently, 10L of oxygen was provided via non-rebreathing mask (FiO₂ 0.8), and the SpO₂ reached 100%. Chest x-ray showed diffuse and increased nodular opacities in both lungs, and computed tomography showed innumerable patchy consolidations/ground glass opacities in both lungs (Fig. 1). Conservative care was provided with 4L of oxygen via nasal prong, 20 mg of Lasix and 2500 mg of tranexamic acid. Two hours after surgery, the patient’s WBC count was 17.0 × 10⁹/L; Hb 15.9 g/dL; platelet count 247 × 10⁹/L; CRP 0.08 mg/dL; and PT INR 1.31. Arterial blood gas analysis with a fraction of inspired oxygen (FiO₂) of 0.36 (O₂ 4L via nasal prong) revealed the following: pH 7.35; arterial carbon dioxide tension (PaCO₂) 41 mmHg; the partial pressure of arterial oxygen (PaO₂) 99.8 mmHg; bicarbonate (HCO₃⁻) 22.0; base excess (BE) –3.1; and arterial oxygen saturation (SaO₂) 96.1%. To exclude other causes of DAH, immunological tests were performed. The immunological results were negative for anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (anti-GBM) antibodies, lupus anticoagulant antibody, β₂-glycoprotein I antibody, double-stranded DNA (dsDNA) antibody, antinuclear antibody (ANA), immunoglobulin E (IgE), immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), anticardiolipin IgG, anticardiolipin IgM, antiphospholipid IgG, antiphospholipid IgM, rheumatoid Factors (C3 and C4), and Coomb test (direct and indirect). ECG data, troponin, and brain natriuretic peptide (BNP) levels were normal. Coagulation profile was near normal. On postoperative day 2, hemoptysis and cough were no longer observed. On postoperative day 5, the patient was discharged. The chest X-ray and computed tomography showed complete resolution of the pulmonary infiltration on postoperative day 14 (Fig. 2).

### 3. Discussion

NPPE is a rare cause of DAH. Studies suggest that the incidence of NPPE among complications of general anesthesia may reach 0.1%.² ³ Postoperative laryngospasm is the commonest clinical scenario in anesthetic practice leading to NPPE⁶ ⁷ and NPPE may occur in up to 4% of all incident laryngospasms.¹⁸ However, a number of other conditions that predispose to upper airway obstruction also lead to NPPE.⁹ ¹¹
The NPPE is related to generation of markedly negative intrathoracic pressure due to forced inspiration against a closed glottis. Negative intrathoracic pressure decreases the right atrial pressure and increases venous return to the right ventricle. The right ventricle is, therefore, distended shifting the intraventricular septum to the left side, which decreases left ventricular compliance. Combined with increased afterload, the results increase the left ventricular end-diastolic pressure and pulmonary capillary wedge pressure. The resulting elevation in pulmonary capillary transmural pressure leads to extravasation of fluid into the alveoli causing pulmonary edema. The pulmonary capillary blood-gas barrier is formed by the capillary endothelium, extracellular matrix, mostly composed of a thin layer of type IV collagen, and the alveolar epithelium. Increased pulmonary capillary transmural pressure causes circumferential stress on the blood-gas barrier and pulmonary capillary wall. Markedly increased transmural pressures ultimately result in stress failure of the blood-gas barrier disrupting the epithelial and endothelial surfaces. Extravasation of blood in addition to fluid results in alveolar hemorrhage.

Remifentanil is widely used in clinical anesthesia due to strong analgesia, rapid onset, short duration, and reduction of cardiovascular response. The administration of a bolus of remifentanil during emergence from general anesthesia may be useful to prevent cough, agitation, and hemodynamic disturbances associated with anesthetic emergence. However, skeletal muscle rigidity occurs following bolus dosing of remifentanil. Severe rigidity of the thoracic and abdominal muscles makes manual ventilation of the lungs difficult. Further, rigidity of the laryngeal muscles may cause closure of the vocal cords, leading to difficult ventilation.

Muscle rigidity and vocal cord closure occur even at low doses of remifentanil in general anesthesia. Kashimoto et al reported that a low doses of remifentanil (0.05 µg·kg⁻¹·min⁻¹) induced muscle rigidity. Kohno et al reported that 3 cases of sudden vocal cord closure during general anesthesia using remifentanil (0.2–0.25 µg·kg⁻¹·min⁻¹). Nakada et al reported that the incidence of difficult ventilation and muscle rigidity after administration of low dose of remifentanil (0.2 µg·kg⁻¹·min⁻¹) was 4%. Also, Schuttler et al reported that 1 patient receiving remifentanil at an initial rate of 0.1 µg·kg⁻¹·min⁻¹ and 8 patients receiving an initial rate of 0.05 µg·kg⁻¹·min⁻¹ experienced muscle rigidity in the immediate postoperative setting. In our case, continuous infusion of 0.2 µg·kg⁻¹·min⁻¹ and bolus dose of 0.37 µg·kg⁻¹ of remifentanil-induced muscle rigidity.

In addition, rapid administration of bolus doses of remifentanil and increase in the infusion rate results in a relatively high incidence of muscle rigidity. The mechanism responsible for opioid-induced muscle rigidity is thought to involve alterations in the central nervous system. One pharmacological investigation has suggested that opioid-induced muscle rigidity is due primarily to the activation of central µ-receptors, whereas δ1 and κ1 receptor attenuate this effect. Remifentanil is a selective µ-opioid receptor agonist. Its rapid plasma effect-site equilibration causes the effect site concentration to rise rapidly and produce a peak in a short time. When applying remifentanil to patients, especially when applying rapid bolus administration or increasing in the infusion rate, attention should be paid to the possible development of muscle rigidity. In the present case, rapid administration of bolus doses of remifentanil (<10 s), even with low doses of remifentanil, may have caused muscle rigidity.

Also, we applied the Naranjo scale sure to calculate the probability of remifentanil-induced muscle rigidity. This adverse drug reaction (ADR) probability scale is a simple method to assess the causality of ADRs in a variety of clinical situations and it has become the most widely employed method since its introduction in 1981. The scale includes 10 questions and their answers can be either “yes,” “no,” or “don’t know.” Each question is rated from –1 to +2. Total score of ≥9 was empirically defined as “definitely,” total score of 5 to 8 being “probably,” total score of 1 to 4 being “possibly,” and the score less than one being “doubtful” having caused the ADR. Our present case was answered “yes” to the question 1, 2, and 3 to score 4, which is “possible” ADR of muscle rigidity from remifentanil according to the Naranjo scale.

Sugammadex, a modified gamma-cyclodextrin, is a novel selective agent that can reverse rocuronium-induced neuromuscular blockade and is well known for affirmatively reducing the postoperative pulmonary complications associated with residual...
neuromuscular blockade. However, there are reports of sugammadex-induced laryngospasm, causing NPPE.\[26–28\]

The sensitivity of upper airway muscle and diaphragm to muscle relaxant is different. Sugammadex may cause the dissociated recovery from the neuromuscular agent between the upper airway smooth muscle and respiratory muscles such as the diaphragm. Sugammadex may trigger negative intrathoracic pressure by raising rapid and efficacious respiratory muscle strength in upper airway obstruction, which may lead to NPPE.

In the present case, remifentanil may have induced muscle rigidity, causing sudden adduction of vocal cords or supraglottic obstruction by soft tissue, resulting in upper airway obstruction. Sugammadex may have induced a dissociated reversal of neuromuscular blockade between the upper airway smooth muscle and respiratory muscles, which has a low response to muscle relaxants. Rapid and effective increase in respiratory muscle strength by sugammadex in the upper airway obstruction via reaction with remifentanil may cause negative intrathoracic pressure. The upper airway obstruction per se also causes excessive inspiratory efforts, leading to negative intrathoracic pressure. The marked negative intrathoracic pressure results in NPPE-related DAH. NPPE-related DAH occurs more often in healthy young men due to their ability to generate profound negative intrathoracic pressure.\[24\]

In the present case, the patient was a 25-year-old healthy male (173 cm, 81 kg, BMI 27.0).

In conclusion, the possibility of upper airway obstruction and NPPE-related DAH should be considered when using a bolus of remifentanil and sugammadex during emergence from general anesthesia.

**Author contributions**

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