Midazolam and Remifentanil by Bolus Injection for Intensely Stimulating Procedures of Brief Duration: Experience with Awake Laryngoscopy

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Laryngoscopy and tracheal intubation are intensely stimulating, usually brief procedures. Successful awake laryngoscopy in the patient with a potentially difficult airway requires both blunting of airway reflexes and maintenance of oxygenation and ventilation. Remifentanil, although typically administered by continuous infusion, may be useful by bolus injection for such intensely stimulating brief procedures.

Although fiberoptic technology has had a favorable impact on awake tracheal intubation for the patient with a potentially difficult airway (1), it is time consuming and requires specialized equipment and extensive topical anesthesia or nerve blocks (2). In addition, the patient with a suspected difficult airway who undergoes fiberoptic tracheal intubation may become needlessly labeled as a "difficult airway." The ability to safely assess a patient using awake, direct laryngoscopy eliminates the need for fiberoptic intubation in some cases and provides valuable information about the ability to visualize the larynx by simple direct laryngoscopy for future anesthetics.

We report a patient for whom bolus injection of midazolam and remifentanil provided favorable conditions for awake, direct laryngoscopy. The patient had a congenital syndrome associated with a craniofacial abnormality. The patient tolerated laryngoscopy well and followed commands to breathe during and immediately after tracheal intubation. The potential advantages and disadvantages of bolus dose remifentanil, including pharmacokinetic simulations, are reviewed.

A 31-yr-old, 172 cm, 78 kg, woman with craniofacial abnormalities was scheduled for repair of an umbilical hernia. She had never undergone direct laryngoscopy and her syndrome was associated with mandibular retrognathia and micrognathia. The patient's Mallampati classification was II/IV and her thyromental distance was 30 mm with mandibular hypoplasia. She had normal cervical spine flexion and atlanto-axial extension. She denied having prior operations or anesthetics. She denied a history of reflux and she had been fasting for more than 12 hours at the time of surgery. An awake laryngoscopy was planned to assess the airway prior to induction of anesthesia.

The patient received 2 mg (26 $\mu g \cdot kgl^{-1}$) of IV midazolam as a premedication. After breathing 100% oxygen for approximately 3 min through a well-sealed facemask, the patient was given IV remifentanil, 250 μg (3.2 $\mu g \cdot kgl^{-1}$) as a bolus injection. Approximately 90 s later, direct laryngoscopy was performed using a #2 Miller laryngoscope blade. With the vocal cords well visualized, a 7.0-mm endotracheal tube was placed under direct vision. The patient remained conscious and followed commands throughout laryngoscopy. Immediately after placement of the endotracheal tube, the patient followed commands to breathe. She was subsequently given propofol 120 mg for anesthetic induction. During laryngoscopy, the patient's Spo_2 remained between 96% and 99%. The heart rate varied from 65–80 bpm and systolic arterial blood pressure ranged from 100–140 mm Hg. After surgery, the patient had no recall of the awake laryngoscopy and subsequent intubation.

In the event of a failed intubation after the remifentanil bolus, our plan was to allow the patient to recover from the remifentanil bolus and proceed with an awake fiberoptic intubation. In the event of a failed intubation and loss of consciousness with poor oxygenation, emergency airway equipment (including a face mask and bag, laryngeal mask airway, oral and nasopharyngeal airways, a transtracheal jet ventilator, and naloxone) was immediately available.

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Using pharmacokinetic simulations, we plotted the midazolam and remifentanil effect-site concentrations (C_e) versus time according to the doses administered to this patient (Fig. 1). Simulations were performed using pharmacokinetic simulation software (STANPUMP, Stanford University, Palo Alto, CA). The pharmacokinetic variables for midazolam and remifentanil were reported by Greenblatt et al. (3) and Minto et al. (4) respectively. The simulations revealed that the peak C_e for midazolam and remifentanil were 19.7 ng/mL and 14.7 ng/mL respectively. Midazolam required more time to reach a maximum C_e and persisted longer than the remifentanil. The time from drug administration to peak effect for midazolam and remifentanil were 9.7 and 1.5 min, respectively.

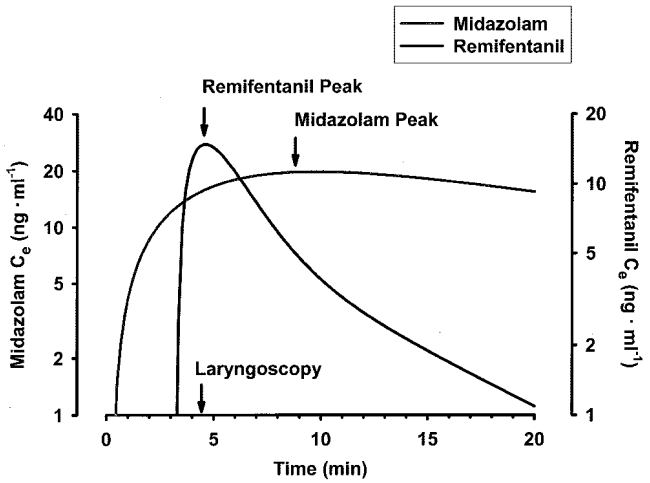

Figure 1. Simulation of the effect site concentrations (Ce) that result from an IV 2 mg (26 μg · kg-1) bolus dose of midazolam followed three minutes later by an IV 250 μg (3.2 μg · kg-1) bolus dose of remifentanil to a 78 kg female.

Discussion

Awake direct laryngoscopy is an intensely stimulating procedure that is typically performed for patients with known or suspected difficult airways. Anesthesiologists are understandably concerned about the loss of spontaneous ventilation and protective airway reflexes that may occur when IV drugs are used to blunt the response to direct laryngoscopy. Thus direct laryngoscopy has largely been replaced by fiberoptic tracheal intubation in approaching patients with difficult airways. An awake look (i.e., direct laryngoscopy for tracheal intubation in the awake, spontaneously ventilating patient), however, is an alternative to fiberoptic tracheal intubation that may offer advantages in some clinical settings. For example, an awake look can be performed rapidly, providing valuable information about the patient's airway for future anesthetics.

Remifentanil by bolus injection, because of its unique pharmacokinetic characteristics, can provide intense analgesia without prolonged respiratory depression or loss of consciousness. Remifentanil's high lipid solubility and relatively high unbound unionized fraction at physiologic pH result in peak C_e within 1–2 minutes after bolus administration (5,6). Likewise, distribution and widespread esterase metabolism of remifentanil allow for early offset and return of spontaneous ventilation (7).

The potential dangers and dose selection nuances when using remifentanil by bolus injection merit discussion. Some of these include the potential for rigidity, respiratory depression, loss of consciousness, and the influence of a benzodiazepine on the adverse effects of remifentanil.

Prior work by Jhaveri et al. (8) studied the effects of a wide range of remifentanil doses on loss of consciousness and muscle rigidity. They found that the median dose of remifentanil required to achieve loss of consciousness when administered as a continuous infusion over 2 minutes was 12 μg/kg. In their work, none of the patients receiving a dose of 5 μg/kg or less lost consciousness (we administered 3.2 μg/kg). In terms of muscle rigidity, they assessed the chest wall, abdominal wall, and extremity muscle mobility and used a scale of none, mild, moderate, and severe. They found that none of the patients receiving <4 μg/kg developed severe muscle rigidity, but several did develop mild-to-moderate rigidity. Additionally, preliminary work assessing the respiratory effects and analgesia of remifentanil bolus administration reported that no muscle rigidity was observed over a bolus dose range of 25 to 200 μg in volunteers (9). Another concern with opioid-induced rigidity is that when a patient is rigid, ventilation may become inadequate and lead to poor oxygenation. Although no work examining this question is available for remifentanil, Streisand et al. (10) evaluated the ability to ventilate volunteers who had become rigid after receiving 15 μg/kg of fentanyl and found that no subject developing rigidity required neuromuscular blockade to ventilate and oxygenate adequately.

No work has examined the influence of midazolam on remifentanil-induced rigidity. However, Neidhart et al. (11) studied the impact of midazolam on fentanyl-induced rigidity. They found that with fentanyl doses of 10 μg/kg or less midazolam (75 μg/kg) prevented rigidity and at fentanyl doses of 15 to 20 μg/kg midazolam attenuated but did not prevent fentanyl-associated rigidity.

Nuances regarding the dosing of remifentanil deserve discussion. Prior work by Minto et al. (4) has demonstrated that elderly patients require less remifentanil as a result of altered pharmacokinetics and pharmacodynamics. From ages 20 to 85, they reported a substantial reduction in central compartment volume and clearance and a 50% reduction in

EC_{50} and the k_{eo}. They also reported that adjusting their pharmacokinetic models to lean body mass improved model performance; this was confirmed in a separate study by Egan et al. (12). These results suggest that the dosing of remifentanil should be adjusted to the lean body mass and that elderly patients (patients over 65 years of age) require as much as 50% to 70% dosage reduction.

In summary, our case report and pharmacokinetic simulation presents an approach to an awake laryngoscopy using bolus administration of midazolam and remifentanil. The technique described provides intense levels of analgesia while the patient remains conscious and responds to commands. Although the respiratory drive was suppressed, the patient remained awake and responded to verbal prompting to breathe and maintained adequate oxygenation. This feature may make it preferable to other techniques using IV sedative hypnotics (e.g., propofol) that render the patient apneic, unconscious, with minimal analgesia or potent inhaled anesthetic (e.g., sevoflurane) that render the patient unconscious yet breathing spontaneously. Prior work has suggested that when preparing a dosing regimen for remifentanil, one should adjust the dose to account for lean body mass and age. Given the pharmacokinetic profile of remifentanil, which allows a rapid return of spontaneous ventilation, it is an attractive choice for intensely stimulating procedures of brief duration such as laryngoscopy.

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