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CASE REPORT

Sedation with a remifentanil infusion to facilitate rapid awakening and tracheal extubation in an infant with a potentially compromised airway

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Abstract: Sedation is generally required during endotracheal intubation and mechanical ventilation in infants and children. While there are many options for the provision of sedation, the most commonly used agents such as midazolam and fentanyl demonstrate a context-sensitive half-life, which may result in a prolonged effect when these agents are discontinued following a continuous infusion. We present a 20-month-old infant who required endotracheal intubation due to respiratory failure following seizures. At the referring hospital, multiple laryngoscopies were performed with the potential for airway trauma. To maximize rapid awakening and optimize respiratory function surrounding tracheal extubation, sedation was transitioned from fentanyl and midazolam to remifentanil for 18–24 hours prior to tracheal extubation. The unique pharmacokinetics of remifentanil are presented in this study, its use in this clinical scenario is discussed, and its potential applications in the pediatric intensive care unit setting are reviewed.

Keywords: remifentanil, sedation, pediatric, airway, extubation

Introduction

Infants and children generally require sedation to alleviate pain and agitation during mechanical ventilation.[1,2] In patients with a known or suspected difficult or critical airway, additional precautions may be needed when they are deemed ready for tracheal extubation. It is particularly important to ensure that tracheal extubation occurs at a time when the residual effects of sedation have abated to avoid any impact that these agents may have on upper airway control and respiratory function. Further, the avoidance of agitation with the potential for additional airway trauma during the awakening process is key in this setting. In the pediatric intensive care unit (PICU), midazolam, fentanyl, and morphine are commonly used to provide sedation and analgesia during endotracheal intubation and mechanical ventilation. Although generally effective, these agents demonstrate a context-sensitive half-life so that the duration of their effects may be lengthy following prolonged infusions.[3,4] As such, following discontinuation of these medications, it is difficult to predict when the patient will be appropriately awake and alert for tracheal extubation. On the other hand, there is a risk of inadvertent tracheal extubation if sedation and analgesia are not adequate. We report a 20-month-old with a history of difficulties with endotracheal intubation at the referring hospital who required sedation during mechanical ventilation for 24–36 hours to allow for resolution of airway edema and coordination of services to allow for a controlled attempt at tracheal extubation. The ultrashort-acting synthetic opioid, remifentanil, was used to provide sedation and yet allow for rapid awakening without concerns of

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a context-sensitive half-life. The basic pharmacokinetics of remifentanil are discussed, previous reports of its use of sedation during mechanical ventilation are reviewed, and clinical recommendations for its use in this scenario are presented.

Case report

Institutional review board approval as well as written informed consent is not required for individual case reports at Nationwide Children's Hospital (Columbus, OH, USA). A 20-month-old, 11 kg toddler with shunted congenital hydrocephalus and absent septum pellucidum presented with respiratory failure secondary to status epilepticus. The patient initially presented to a referring hospital where he was noted to have a difficult airway that required five attempts to achieve endotracheal intubation. Ultimately, his airway was secured with an uncuffed 4–0 mm endotracheal tube. The reasons for the multiple intubation attempts were unclear, as there were no reports of airway problems during prior anesthetic events for ventriculoperitoneal shunt placement during the neonatal period. On arrival, the patient's hemodynamic and respiratory status were stable. Physical examination was notable for moderate micrognathia. Sedation during mechanical ventilation was initiated with continuous infusions of fentanyl at 2 µg/kg/h and midazolam at 0.15 mg/kg/h. Following a 2-day PICU course, the patient's clinical status improved and he was deemed ready for tracheal extubation from respiratory and neurologic perspectives. However, even after a 24-hour course of dexamethasone for presumed airway edema, there was no air leak around the endotracheal tube at a peak inflating pressure of 30 cm H_2O. The pediatric otorhinolaryngology (ear, nose, and throat) service was consulted to evaluate his airway and a decision was made to attempt tracheal extubation the next morning in the PICU. For approximately 18 hours prior to the scheduled time for tracheal extubation, sedation was transitioned from midazolam and fentanyl to remifentanil. The patient was started on remifentanil at a dose of 0.1 µg/kg/min. Dose adjustments were made in increments of 0.05 µg/kg/min as needed. An initial infusion dose of 0.2 µg/kg/min was required to achieve an adequate level of sedation. Dose increases were made twice over the ensuing 9 hours to a maximum dose of 0.3 µg/kg/min. There were no hemodynamic or respiratory adverse effects during the remifentanil infusion. The following day, with both the intensive care unit (ICU) and otorhinolaryngology teams at the bedside, the remifentanil infusion was discontinued. Within 10 minutes, the patient was alert and active with spontaneous eye opening. His trachea was extubated uneventfully, although he subsequently developed moderate

stridor and retractions. These were responsive to treatment with racemic epinephrine aerosols, high-flow nasal cannula, and heliox. A nasopharyngeal fiber optic examination at the bedside showed moderate laryngeal edema. The stridor resolved over the next 24 hours and the patient was weaned to room air, after which he was transferred to the inpatient ward and eventually discharged home.

Discussion

Remifentanil was the last of the current clinically available piperidine, synthetic opioid derivatives, introduced into clinical practice. Its potency and respiratory depressant effects are approximately twice that of fentanyl; however, its clinical half-life is significantly shorter.[5,6] Its rapid metabolism is the result of the incorporation of a methyl-ester ring into the molecule, which allows for hydrolysis by nonspecific plasma and tissue esterases. Its molecular configuration and rapid metabolism result in a unique pharmacodynamic profile with a rapid onset, easy titration by continuous infusion, and a short context-sensitive half-life with rapid elimination across all age groups regardless of the infusion characteristics.[7,8] Owing to its predictable characteristics, it has become an effective agent in the neonatal population, allowing the provision of intense analgesia/anesthesia, a rapid recovery profile, and little to no residual effect on respiratory function.[9–12]

Although a frequently used agent for the provision of intraoperative anesthesia, to date, there are limited reports regarding its use for sedation during mechanical ventilation (Table 1).[13–21] The limited data available demonstrate its efficacy for sedation during mechanical ventilation in the adult, pediatric, and neonatal population with limited adverse physiologic effects. Its sedative effects have been shown to be comparable to those of fentanyl or morphine with a more rapid recovery and weaning from mechanical ventilation. In the patient that we presented, remifentanil provided adequate sedation with rapid dissipation of its effects when the infusion was discontinued to eliminate the potential impact of residual sedation on upper airway and respiratory function in patient with a compromised airway. Further, it allowed for adequate sedation right up to the point of tracheal extubation, minimizing the likelihood of agitation-related airway trauma.

The adverse effect profile of remifentanil is similar to that of other synthetic opioids and includes dose-dependent respiratory depression, bradycardia, and hypotension. Hemodynamic effects are unusual except in the setting of hypovolemia. Furthermore, it should not be used in a patient who has received opioids for a prolonged period of time

Table 1 Previous reports of remifentanil use in the intensive care unit population

Reference	Demographic data	Remifentanil dosing regimen	Conclusion
Breen et al[13]	One hundred and five adult patients requiring mechanical ventilation for up to 10 days. Medical or postsurgical comorbidities	Starting dose: 6–9 µg/kg/h Titrate: ±1.5 µg/kg/h every 5–10 min	Remifentanil reduced the duration of mechanical ventilation by 53.5 hours compared to the control group sedated with midazolam and fentanyl/morphine. Remifentanil was well tolerated and administered for up to 10 days. The safety profile was thought to be similar to that of other sedation regimens
Muellejans et al[14]	Eighty adults requiring mechanical ventilation following cardiac surgery. Comparison of remifentanil–propofol vs midazolam–fentanyl	Starting dose: 6–12 µg/kg/h to a maximum of 60 µg/kg/h. Propofol 0.5–4.0 mg/kg/h if sedation was inadequate	Remifentanil-based regimen reduced the time on mechanical ventilation (20.7±5.2 vs 24.2±7 hours, $P<0.05$) and intensive care unit length of stay (46.1±22 vs 62.4±27.2 hours, $P<0.05$) compared to fentanyl–midazolam
Akinci et al[15]	Twenty-two children who required mechanical ventilation following orthopedic spinal surgery	Starting dose: 0.1 µg/kg/min. Rate adjusted up or down by 25% of starting rate	Remifentanil and fentanyl were comparable in providing suitable analgesia/sedation based upon Behavioral Pain Scale and Riker's Sedation–Agitation Scale. There was no difference between the two groups in adverse events
Welzing et al[16]	Twenty-four mechanically ventilated infants with a gestational age >36 weeks and a postnatal age <60 days admitted to the pediatric intensive care unit for respiratory failure	Starting dose: 9 µg/kg/h. Titration: ±3 µg/kg/h. Maximum dose: 30 µg/kg/h. All patients also received midazolam 50 µg/kg/h (maximum dose: 400 µg/kg/h) and were randomized to remifentanil or fentanyl	Time to tracheal extubation following discontinuation of the opioid infusion was shorter: 80 minutes (IQR 15–165) with remifentanil compared to fentanyl group: 782 minutes (IQR 250.8–18750)
Welzing et al[17]	Two hundred and forty-three mechanically ventilated infants with a gestational age >36 weeks and a postnatal age <60 days admitted to the pediatric intensive care unit for respiratory failure	Starting dose: 9 µg/kg/h. Titration: ±3 µg/kg/h. Maximum dose: 30 µg/kg/h All patients also received midazolam 50 µg/kg/h (maximum dose: 400 µg/kg/h)	Fentanyl group required a 47% increase in dose compared to 24% increase of the remifentanil to maintain adequate sedation levels. Sentence clarification: No opioid withdrawal noted and patients in both groups had low average Finnegan scores.
Giannantonio et al[18]	Forty-eight preterm infants born at ≤37 weeks gestational age requiring mechanical ventilation for respiratory failure	Starting dose: 0.075 µg/kg/min Maximum dose: 0.94 µg/kg/min	97% of patients received adequate sedation and analgesia based upon Neonatal Infant Pain Scale and COMFORT scores. Time from discontinuation of remifentanil to extubation was 36±12 minutes. No adverse respiratory or cardiovascular effects were observed.
Silva et al[19]	Twenty preterm neonates (28–34 weeks gestational age) requiring mechanical ventilation for respiratory distress syndrome	Starting dose: 0.5 µg/kg/min. Patients randomized to either morphine or remifentanil	Both morphine and remifentanil provided adequate sedation and analgesia based upon Neonatal Infant Pain Scale and COMFORT scores. Following opioid discontinuation, time to infant awakening and tracheal extubation was 18.9 and 12.1 times faster with remifentanil compared to morphine.
Cavaliere et al[20]	Ten adults requiring mechanical ventilation	Starting dose: 0.02 µg/kg/min. Infusion increased to 0.05, 0.10, 0.15, 0.20, and 0.25 µg/kg/min every 30 minutes.	Infusion rates up to 0.05 µg/kg/min provided effective sedation. Adverse respiratory and cardiovascular effects noted at higher doses.
Dahaba et al[21]	Forty adults requiring mechanical ventilation	Remifentanil 0.15 µg/kg/min or morphine 75 µg/kg/min	Time in optimal sedation range was higher in the remifentanil group with less frequent infusion rate adjustments. The duration of mechanical ventilation and extubation time were significantly longer in the morphine group. More subjects in the morphine group than in the remifentanil group required midazolam. The incidence of adverse events was low and comparable in the two groups

as the rapid decrease in plasma opioid concentration upon discontinuation may result in withdrawal. A unique effect specific to the synthetic opioids is chest wall and laryngeal rigidity.[22,23] These effects are related to the dose and rate of administration, and are centrally mediated responses that can interfere with respiratory function. The effect can be reversed with naloxone or interrupted with neuromuscular blocking agents. Although rare, occurrence of chest wall and laryngeal rigidity should be considered if respiratory dysfunction is noted following the administration of synthetic opioids, as such an effect may interfere with respiratory function and result in rapid oxygen desaturation and hypoxemia. To limit the incidence of such issues, a bolus dose should be infused around 2 to 3 minutes as more rapid infusion can cause chest wall rigidity. One other concern with remifentanil is the potential for the rapid development of tachyphylaxis and hence the need to rapidly escalate the dose even during short-term infusions of 24–48 hours. Although suggested in the literature, studies of its use in the ICU for sedation do not uniformly demonstrate this phenomenon.[24,25] Furthermore, recent animal and retrospective human data have suggested that there may be long-term neurocognitive effects of various sedative agents, including those acting through the γ-amino butyric acid or *N*-methyl-D-aspartate systems.[26] Although prospective studies in humans have failed to validate this concern, opioids have not been included in the groups of agents shown to be proapoptotic and responsible for these changes in animal studies.

With these caveats in mind, we believe that the rapid onset and offset of remifentanil may make it a useful agent for the short-term sedation of patients during mechanical ventilation in the ICU setting. The technique may be particularly applicable to various clinical situations where rapid weaning and tracheal extubation are desired, such as the patient with a difficult airway. Given the cost constraints and the potential for tachyphylaxis, we believe that remifentanil should be used only for short-term sedation (48–72 hours) and specific clinical scenarios. In our practice, remifentanil is most commonly used for mechanically ventilated patients who require frequent neurologic assessments due to traumatic brain injury or in patients, such as the subject of this report, with airway concerns for providing a deep sedation and yet allowing for rapid awakening. Our experience would suggest a starting dose of 0.1 µg/kg/min with increments of 0.05–0.1 µg/kg/min as needed to achieve the desired depth of sedation. If the patient is already receiving other agents, the remifentanil can be started and then the other agents can be decreased or discontinued.

Disclosure
The authors declare no conflicts of interest in this work.

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