PEDIATRIC PHARMACOTHERAPY

Remifentanil Use in Infants and Children
Marcia L. Buck, Pharm.D., FCCP, FPPAG

Remifentanil, a μ-opioid agonist with a rapid onset and short duration of action, has become a valuable component of general anesthesia in infants, children, and adults since it was approved by the Food and Drug Administration in 1996.[1,2] Although it is not yet approved for procedural or postoperative analgesia in infants or children, a growing number of recent studies suggest that remifentanil has the potential to be of benefit in these settings as well.

Mechanism of Action
Remifentanil is a synthetic 4-anilidopiperidine opioid with greater affinity for μ-opioid receptors compared to δ and κ receptors. It has been suggested to be equal to or up to twice the potency of fentanyl and approximately one-tenth the potency of sufentanil, but equivalency has not been well established. The effects of remifentanil are antagonized by naloxone.[1-3]

Pharmacokinetics and Pharmacodynamics
The pharmacokinetic profile of remifentanil has been described in adults as well as pediatric patients. Remifentanil clearance has been fit to a three-compartment model, with a rapid distribution half-life of 1 minute, a slower distribution phase with a half-life of 6 minutes, and a terminal elimination half-life of 10-20 minutes. The resulting context-sensitive (biologic) half-life ranges from 3 to 10 minutes. In adults, remifentanil has an initial volume of distribution of 100 mL/kg resulting from rapid perfusion of peripheral tissues. At steady-state, the average volume of distribution is 350 mL/kg. Remifentanil is 70% bound to plasma proteins, primarily alpha-1-acid-glycoprotein.[2]

Remifentanil is metabolized by nonspecific esterases in the blood and tissues. Esterase-mediated hydrolysis results in production of a nearly inactive carboxylic acid metabolite which is excreted by the kidneys. The metabolite has an elimination half-life of approximately 90 minutes. In adults, remifentanil has an estimated clearance of 40 mL•kg/min. Renal or hepatic dysfunction has no significant effects on remifentanil clearance.[2]

The rapid onset of remifentanil is the result of a time for blood-brain equilibration of only 1-2 minutes. Infusions of 0.05-0.1 mcg/kg/min produce analgesia with blood concentrations of 1-3 ng/mL. The short elimination half-life produces a brief duration of action, with recovery in most patients occurring within 5 to 10 minutes after dose administration. The rapid clearance also prevents drug accumulation, so that unlike other opioids the duration of action of remifentanil does not increase with prolonged administration.[2]

Several studies have evaluated remifentanil pharmacokinetic parameters in infants and children. In the first of a series of studies by Davis and colleagues, six infants from 5 to 60 days of age were given a single remifentanil dose of 5 mcg/kg.[4] Mean clearance and volume of distribution were 80 mL/kg/min and 325 mL/kg, very similar to values reported in adults. A subsequent study in a larger sample allowed the authors to identify age-related changes in remifentanil kinetics.[5] Forty-two infants and children (neonates-18 years of age) received a single 5 mcg/kg dose during elective surgery; 34 patients had complete data for analysis. The volume of distribution was largest in infants less than 2 months of age, 452.8 ± 144.7 mL/kg, and declined with increasing age to 242.5 ± 109.2 mL/kg in the patients between 16 and 18 years. Clearance was more rapid in the infants less than 2 months (90.5 ± 36.8 mL•kg/min) and those 2 months to 2 years of age (92.1 ± 25.8 mL•kg/min) compared to the other groups (means 46.5-76.0 mL•kg/min). Half-life was similar among the groups, ranging from 3.4 to 5.7 min.

In 1999, these investigators gave a single 5 mcg/kg remifentanil dose to 12 children (10 months-15 years of age) undergoing cardiac surgery to evaluate the impact of cardiopulmonary bypass (CPB) on drug

elimination.[6] While volume of distribution was not affected by CPB (234.5 $\pm$ 105.5 mL/kg before and 235.5 $\pm$ 10.2 mL/kg after), clearance was increased by 20% (38.7 $\pm$ 9.6 mL•kg/min before compared to 46.8 $\pm$ 14 mL•kg/min, p < 0.05). The authors noted that the relatively small impact of CPB on remifentanil may be an advantage compared to other opioids known to be more highly affected. These results have been challenged by another group of investigators in a 2009 study of nine children (0.5 to 4 years of age) in which volume of distribution after CPB was increased up to 2.41 times pre-CPB values.[7]

Rigby-Jones and colleagues studied remifentanil pharmacokinetics in 26 children (1 month-9 years) after cardiac surgery.[8] On arrival to the pediatric intensive care unit, all patients received a 50 mcg/kg/hr midazolam infusion with remifentanil initiated at a rate of 0.8 mcg/kg/min. After 1 hr, the rate was decreased by 0.1 mcg/kg/min increments every 20 minutes until the patient awoke. At completion of the study, patients were switched to morphine for long-term sedation. Using mixed-effects population modeling, clearance was approximated at 68 mL/kg/min, with a volume of distribution of 141 mL/kg, confirming the results of earlier studies.

Clinical Experience
The safety and efficacy of remifentanil as a component of general anesthesia in infants and children has been established in a wide range of studies.[1,2] In both open-label and blinded comparison trials, remifentanil infusions of 0.05 to 1 mcg/kg/min, with bolus doses of 1 mcg/kg, produced effective analgesia while maintaining hemodynamic stability. The short duration of action provided a rapid recovery, with a median time to extubation ranging from 8 to 13 minutes.

Based on the success of remifentanil during surgery, its use quickly expanded to pediatric patients requiring procedural sedation as well as those undergoing intubation and mechanical ventilation.[1,9,10] For more than a decade, case series and small-scale clinical trials have explored the efficacy of remifentanil in these settings. Remifentanil has been used for sedation and analgesia in infants and children undergoing flexible bronchoscopy[11], endoscopy[12], cardiac electrophysiology studies for catheter ablation[13], laser surgery for retinopathy of prematurity[14], bone marrow aspiration[15], and sedation for CT or MRI studies.[16]

Over a dozen studies have evaluated remifentanil for endotracheal intubation in infants and children.[1,9,10] An assortment of methodologies have been used, with a dosing range of 1-4 mcg/kg. Several authors have proposed an optimal dose of 2-3 mcg/kg. To address this issue, Hume-Smith and coworkers evaluated age-specific remifentanil intubating doses in 64 infants and children.[17] Patients were stratified into three groups: I (0-3 months), II (4-12 months), and III (1-3 years). Following a 10 mcg/kg dose of glycopyrrolate and 5 mg/kg of propofol, patients received a remifentanil dose of 1-6 mcg/kg. Tracheal intubation was successful in 85%, 63%, and 75% of patients, with an effective dose in 50% of patients (ED_{50}) for the three groups of 3.1 (95% CI 2.5-3.8), 3.7 (2.0-5.4), and 3.0 (2.1-3.9) mcg/kg, respectively. The children in group III had a longer duration until return of spontaneous respiration than the infants (221 sec compared to 180 sec, p < 0.05).

Two recent trials have compared remifentanil to other opioids for intubation in neonates. Choong and colleagues randomized 30 neonates to receive remifentanil 3 mcg/kg or the combination of fentanyl 2 mcg/kg and succinylcholine 2 mg/kg.[18] Both groups received atropine 0.02 mcg/kg. Median time to intubation was similar in both groups (4.1 min in the remifentanil group vs 2.6 min in the fentanyl group, p = 0.88). There were no differences in the secondary outcomes assessed, including total laryngoscopic time, time to return of spontaneous respirations, heart rate, blood pressure, oxygen saturation, number of intubation attempts, or percentage of patients intubated on the first attempt. There were no significant differences in adverse effects. Chest wall rigidity occurred in two patients, both of whom received remifentanil. The authors concluded that remifentanil may be a viable option for intubation in some neonates, but that a 3 mcg/kg dose may be associated with a risk for chest wall rigidity.

Norman and colleagues compared a traditional regimen of atropine and morphine to rapid sequence intubation (RSI) in 34 preterm infants.[19] Patients were randomized to receive either atropine (0.01 mg/kg) and morphine (0.3 mg/kg) or RSI with glycopyrrolate (5 mcg/kg), thiopental (2-3 mg/kg), succinylcholine (2 mg/kg), and remifentanil (1 mcg/kg). Intubating conditions were evaluated according to a scoring system including ease of laryngoscopy, position of the vocal cords, coughing, jaw relaxation, and limb movement.

Good intubating conditions were present in 16/17 patients in the RSI group compared to only one patient in the atropine/morphine group. Median intubation scores were 5 and 12 in the two groups, respectively (p<0.001). Infants in the atropine/morphine group had a prolonged heart rate decrease and mean arterial pressure increase during intubation, with a subsequently lower blood pressure assessed 3 hours after intubation. Plasma cortisol and pain scores were no different between the groups, but the morphine group had a prolonged period of central nervous system

depression as assessed by electroencephalogram. The authors concluded that RSI may provide better intubating conditions and less adverse hemodynamic effects in preterm infants than traditional regimens.

Several papers have evaluated the use of remifentanil for sedation during mechanical ventilation in the pediatric population. In the Rigby-Jones study described earlier, the combination of remifentanil and midazolam infusions produced satisfactory sedation scores in infants and children following cardiac surgery.[8] One patient developed hypotension following the start of the remifentanil infusion, with a decrease from 71/47 to 59/39 mm Hg in 3 minutes. Two minutes after discontinuation of remifentanil, the patient's blood pressure had returned to baseline.

In 2009, Giannantonio and colleagues described the use of remifentanil in a group of preterm neonates requiring mechanical ventilation.[20] The authors evaluated 48 patients. Therapy was initiated with an infusion of 0.075 mcg/kg/min. Patients were monitored with Neonatal Infant Pain Scale (NIPS) and Comfort scale scores. NIPS scores range from 0 (no pain) to 7 (severe pain), while the Comfort scores fall into one of three ranges: 8-16 (deep sedation), 17-26 (light sedation), and 27-40 (inadequate sedation). Goals for the study were NIPS scores of 3 or less and Comfort scores of 16 or less. Assessments were made at the start of treatment, at 1, 3, and 6 hours, and every 6 hours until discontinuation.

Remifentanil produced the target level of analgesia and sedation in 97% of the neonates within 12 hours. NIPS scores decreased soon after the start of therapy, with a mean of 6.3 $\pm$ 1.9 at baseline and 4.1 $\pm$ 1.9 at 1 hr post-treatment. At 24 hours, the mean NIPS score had declined to 1.7 $\pm$ 0.7 and remained at that level throughout the remainder of therapy. Comfort scores showed a similar improvement, decreasing from a mean baseline score of 30.7 $\pm$ 3.7 to 13.7 $\pm$ 3.8 at 24 hrs. None of the patients required additional sedation or analgesia during the study, but dose increases were necessary in 73%, suggesting the possibility of tolerance. Mean duration of therapy was 5.9 $\pm$ 5.7 days. Time to extubation after discontinuation was 36 $\pm$ 12 min.

Welzing and coworkers used a short course of remifentanil and propofol to aid in weaning pediatric intensive care patients from mechanical ventilation.[21] Twenty-three children (3 months-10 years of age) had their fentanyl and midazolam infusions replaced by the two shorter-acting agents during the final phase of weaning. The combination allowed a rapid transition from a sedated state to spontaneous respiration, protective airway reflexes, and an appropriate level of alertness. Mean extubation time after

stopping the remifentanil-propofol combination was 24 $\pm$ 20 min.

Warnings and Precautions
Like other opioids, remifentanil produces dose-dependent apnea, respiratory depression, hypotension, and bradycardia. Peak hemodynamic effects typically occur within 3-5 minutes of initiation or a dose adjustment. A dose or concentration-dependent decrease in mean arterial pressure has been demonstrated in several studies.[2,22] In the Ross study conducted with high-dose remifentanil (5 mcg/kg), 17% of the 42 children developed hypotension.[5]

Skeletal muscle rigidity may occur after administration of remifentanil doses greater than 1 mcg/kg or infusion rates greater than 0.1 mcg/kg/min. Management consists of respiratory support, remifentanil rate reduction or discontinuation, or administration of a neuromuscular blocking agent.[1,2] The incidence of skeletal muscle rigidity has not been established, as many of the case reports have contained insufficient detail to establish causality.

Adverse Effects
The most frequently reported adverse effects during the pediatric trials of remifentanil conducted prior to marketing were vomiting (12-16%), nausea (6-8%), shivering or rhonchi (3%), stridor and cough (1%).[2] The results were similar to those reported in the comparison groups receiving fentanyl, as well as those observed in trials in adults. Post-marketing adverse effect reports include seizures, arrhythmias, and hypersensitivity reactions.[2,8,9]

Drug Interactions
Remifentanil should not be administered through the same IV tubing with blood products, in order to avoid hydrolysis of the drug by esterases in the blood products being delivered.[2]

Availability
Remifentanil (Ultiva®) is available in 1 and 5 mg single-use vials. After reconstitution to a 1 mg/mL solution, it may be further diluted to a concentration of 20-250 mcg/mL. Remifentanil is stable for 24 hrs at room temperature when diluted with 5% dextrose, 0.9% or 0.45% sodium chloride, 5% dextrose and 0.9% sodium chloride, or lactated Ringer's with 5% dextrose. If diluted with lactated Ringer's, it is stable for only 4 hrs. Remifentanil may be infused through the same IV tubing with propofol.[2]

Dosage Recommendations
When used for anesthesia, an initial remifentanil 1 mcg/kg bolus dose is typically administered over 30-60 seconds followed by an infusion of 0.25 mcg/kg/min. The infusion may be titrated

between a range of 0.05 to 1.3 mcg/kg/min and supplemented with bolus doses of 1 mcg/kg as needed. Remifentanil is typically used in conjunction with nitrous oxide, halothane, sevoflurane, or isoflurane. Because of the more rapid clearance seen in neonates, a higher remifentanil infusion rate of 0.4 mcg/kg/min may be required for maintenance anesthesia.[2] Similar infusion rates (0.05-1 mcg/kg/min) have been used for procedural sedation or during mechanical ventilation. For infants and children undergoing endotracheal intubation, a dose of 2-3 mcg/kg given over 60 seconds appears to produce optimal intubating conditions in most patients.

Summary

The short duration of remifentanil has made it a valuable addition to the range of anesthetic agents used in pediatric surgery. It may also provide a unique alternative to traditional agents for procedural sedation, intubation, or mechanical ventilation in infants and children.

References

1. Welzing L, Roth B. Experience with remifentanil in neonates and infants. Drugs 2006;66:1339-50.
2. Ultiva® prescribing information. Bioniche Pharma USA LLC, March 2009. Available at www.ultiva.com (accessed 3/30/13).
3. Gelberg J, Jonmarker C, Stenqvist O, et al. Intravenous boluses of fentanyl, 1 μg kg⁻¹, and remifentanil, 0.5 μg kg⁻¹, give similar maximum ventilator depression in awake volunteers. Br J Anaesth 2012;108:1028-34.
4. Davis PJ, Ross AK, Henson LG, et al. Remifentanil pharmacokinetics in neonates [abstract]. Anesthesiology 1997;87(3A):A1064.
5. Ross AK, Davis PJ, Dear GL, et al. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. Anesth Analg 2001;93:1393-401.
6. Davis PJ, Wilson AS, Siewers RD, et al. The effects of cardiopulmonary bypass on remifentanil kinetics in children undergoing atrial septal defect repair. Anesth Analg 1999;89:904-8.
7. Sam WJ, Hammer GB, Drover DR. Population pharmacokinetics of remifentanil in infants and children undergoing cardiac surgery. BMC Anesthesiol 2009;9:5. dio: 10.1186/1471-2253-9-5.
8. Rigby-Jones AE, Priston MJ, Sneyd JR, et al. Remifentanil-midazolam sedation for pediatric patients receiving mechanical ventilation after cardiac surgery. Br J Anaesth 1007;99:252-61.
9. Marsh DF, Hodkinson B. Remifentanil in paediatric anaesthetic practice. Anaesthesia 209;64:301-8.
10. Penido MG, Garra R, Sammartino M, et al. Remifentanil in neonatal intensive care and anaesthesia practice. Acta Paediatr 2010;99:1454-63.
11. Reyle-Hahn N, Migemann B, Max M, et al. Remifentanil and propofol for sedation in children and young adolescents undergoing diagnostic flexible bronchoscopy. Paediatr Anaesth 2000;10:59-63.
12. Drover DR, Litalien C, Wellis V, et al. Determination of the pharmacodynamic interaction of propofol and remifentanil during esophagogastroduodenoscopy in children. Anesthesiology 2004;100:1382-6.
13. Niksch A, Liberman L, Capcich A, et al. Effects of remifentanil anesthesia on cardiac electrophysiologic properties in children undergoing catheter ablation of supraventricular tachycardia. Pediatr Cardiol 2010;31:1079-82.
14. Sammartino M, Bocci MG, Ferro G, et al. Efficacy and safety of continuous intravenous infusion of remifentanil in preterm infants undergoing laser therapy in retinopathy of prematurity: clinical experience. Paediatr Anaesth 2003;13:596-602.
15. Ince IE, Iyilikci L, Yilmaz S, et al. Sedation for short hemato-oncologic invasive procedures in children: comparison of propofol-remifentanil and propofol-fentanyl. J Pediatr Hematol Oncol 2013;35:112-7.
16. Joshi G, Tobias JD. Remifentanil to facilitate high-resolution computed tomography imaging of the chest or magnetic resonance imaging in infants. South Med J 2009;102:1121-4.
17. Hume-Smith H, McCormack J, Montgomery C, et al. The effect of age on the dose of remifentanil for tracheal intubation in infants and children. Pediatr Anesth 2010;20:19-27.
18. Choong K, Al Faleh K, Doucette J, et al. Remifentanil for endotracheal intubation in neonates: a randomized controlled trial. Arch Dis Child Fetal Neonatal Ed 2010;95:F80-F84.
19. Norman E, Wikstrom S, Hellstrom-Westas L, et al. Rapid sequence induction is superior to morphine for intubation of preterm infants: a randomized controlled trial. J Pediatr 2011;159:83-9.
20. Giannantonio C, Sammartino M, Valente E, et al. Remifentanil analgosedation in preterm newborns during mechanical ventilation. Acta Paediatr 2009;98:1111-5.
21. Welzing L, Vierzig A, Junghaenel S, et al. Remifentanil and propofol for weaning of mechanically ventilated pediatric intensive care patients. Eur J Pediatr 2011;170:477-81.
22. Standing JF, Hammer GB, Sam WJ, et al. Pharmacokinetic-pharmacodynamic modeling of the hypotensive effect of remifentanil in infants undergoing cranioplasty. Pediatr Anesth 2010;20:7-18.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their April meeting:

1. Guidelines for the use of albumin were approved.

2. In response to the shortage, the use of sodium bicarbonate for buffering of local anesthetics is no longer permitted.

3. The restrictions on rivaroxaban (Xarelto®) were amended to include all FDA approved indications:

- reduction of the risk for stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE)
- prevention of recurrence of DVT or PE
- prophylaxis of DVT in patients having knee or hip replacement surgery.