Remifentanil
Newborn use only

2021

Alert	Remifentanil is a Schedule 8 drug. Chest wall rigidity has been reported in 10–20% of infants given it as a bolus (over <60 seconds) or at higher dose, particularly in preterm infants. Chest wall rigidity can be treated with naloxone and muscle relaxants.
Indication	1. Premedication for non-emergency intubation; 2. Infusion for analgesia/sedation
Action	Remifentanil is a potent μ receptor agonist with rapid onset of action – peak analgesic action within 1 minute. Rapidly metabolised into inactive metabolites by non-specific plasma esterases with a half-life of 3-5 minutes.
Drug Type	Remifentanil is a synthetic opioid analgesic drug related to fentanyl.
Trade Name	DBL Remifentanil, Remifentanil Alphapharm, Remifentanil APOTEX, Remifentanil-AFT, Ultiva.
Presentation	Remifentanil Powder [remifentanil hydrochloride] for infusion 1 mg, 2 mg, 5 mg. Also contains glycine, hydrochloric acid and/or sodium hydroxide.
Dosage	**Premedication for intubation:** 1 to 3 microgram/kg; may be repeated in 2–3 minutes if needed. **Infusion for analgesia in spontaneously breathing infants:** 0.03 microgram/kg/minute as intravenous infusion [highest safe dose unknown]. **Infusion for analgesia/sedation in ventilated infants:** 0.15–1 microgram/kg/minute as intravenous infusion.
Maximum daily dose	1 microgram/kg/minute.
Route	Intravenous.
Preparation	**IV bolus as premedication for intubation** **STEP 1:** Add 1 mL of water for injection to 1 mg vial of remifentanil to make a 1 mg/mL solution. **STEP 2:** Draw up 0.5 mL (500 microgram) of the above solution and add 9.5 mL glucose 5% or sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 50 microgram/mL. **STEP 3:** From the above solution, draw up 0.2 mL (10 microgram) and add 9.8 mL glucose 5% or sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 1 microgram/mL. **IV infusion for spontaneously breathing infants (≥ 2.5 kg only)** **2-STEP DILUTION** **Prescribed amount:** 200 **microgram**/kg remifentanil and make up to 50 mL with glucose 5% or sodium chloride 0.9% **Infusion rate:** 0.5 mL/hour = 0.03 microgram/kg/min **Step 1:** Add 1 mL of water for injection to 1 mg vial of remifentanil to make a 1 mg/mL solution. **Step 2: From the above solution, draw up 0.2 mL/kg** (200 **microgram**/kg) and further dilute with glucose 5% or sodium chloride 0.9% to make a final volume of 50 mL. Infusing at a rate of **0.5 mL/hour = 0.03 microgram/kg/minute.** **IV infusion for analgesia/sedation in ventilated infants** **2-STEP DILUTION** **Prescribed amount:** 3 mg/kg remifentanil and make up to 50 mL with glucose 5% or sodium chloride 0.9% **Infusion rate:** 1 mL/hour = 1 microgram/kg/minute

	Step 1: Add 1 mL of water for injection to 1 mg vial of remifentanil to make a 1 mg/mL solution. **Step 2: From the above solution draw up 3 mL/kg** (3 mg/kg) and further dilute with glucose 5% or sodium chloride 0.9% to make a final volume of 50 mL. Infusing at a rate of **1 mL/hour = 1 microgram/kg/minute.**
Administration	**IV BOLUS:** Administer over at least 1 minute. Flush with 1 mL of sodium chloride 0.9%. Onset of action is immediate. Half-life is approximately 3–10 minutes. **CONTINUOUS IV INFUSION**: Via syringe driver. Upon ceasing the continuous infusion, flush the line with 1 mL of sodium chloride 0.9% over 1 hour. Note: It is advisable to use a dedicated IV line where possible.
Monitoring	Full cardiorespiratory monitoring. Monitor for urinary retention.
Contraindications	Known hypersensitivity to fentanyl or remifentanil.
Precautions	Rapid injection (<60 seconds) of remifentanil is associated with chest wall rigidity. Remifentanil in a bolus dose of 5 microgram/kg may cause hypotension.
Drug Interactions	Remifentanil enhances the action of other sedatives and hypnotics. Cardiovascular effects may be enhanced by beta blockers and calcium channel blockers.
Adverse Reactions	Respiratory depression, chest wall rigidity (can be treated with naloxone and muscle relaxants), bradycardia and asystole (may respond to atropine), hypotension, postoperative hypertension.
Compatibility	Fluids: Glucose 5%, glucose 5% in sodium chloride 0.9%, sodium chloride 0.9%, sodium chloride 0.45%, water for injection. Not tested with glucose 10%.[19] Y-site: Aciclovir sodium, adrenaline (epinephrine) hydrochloride, alfentanil hydrochloride, amikacin sulfate, aminophylline, amiodarone hydrochloride, ampicillin sodium, azithromycin, aztreonam, buprenorphine hydrochloride, calcium gluconate, cefazolin sodium, cefepime hydrochloride, cefotaxime, cefotetan disodium, cefoxitin, ceftazidime, ceftriaxone sodium, cefuroxime, , ciprofloxacin, clindamycin phosphate, dexamethasone sodium phosphate, digoxin, dobutamine hydrochloride, dopamine hydrochloride, fentanyl, fluconazole, ganciclovir sodium, gentamicin sulfate, heparin sodium, hydrocortisone sodium succinate, imipenem-cilastatin sodium, insulin regular, isoprenaline hydrochloride, lidocaine (lignocaine) hydrochloride, magnesium sulfate, mannitol, methylprednisolone sodium succinate, metoclopramide hydrochloride, metronidazole, midazolam hydrochloride, milrinone lactate, morphine sulfate, netilmicin sulfate, nitroglycerin, noradrenaline (norepinephrine) bitartrate, octreotide acetate, ondansetron hydrochloride, pancuronium bromide, phenylephrine hydrochloride, piperacillin sodium-tazobactam sodium, potassium acetate, potassium chloride, potassium phosphates, ranitidine hydrochloride, rocuronium bromide, sodium acetate, sodium bicarbonate, sufentanil citrate, sulfamethoxazole-trimethoprim, theophylline, thiopental sodium, ticarcillin disodium-clavulanate potassium, tobramycin sulfate, vancomycin hydrochloride, vasopressin, vecuronium bromide, zidovudine.
Incompatibility	Amino acid/glucose and lipid infusion: No information. Propofol, amphotericin, chlorpromazine, diazepam, furosemide (frusemide).
Stability	Reconstituted product should be used promptly and any unused material discarded according to local Schedule 8 drug policy.
Storage	Store below 25° C. The 1 mg presentation should be stored protected from light.
Special Comments	Treat chest wall rigidity with supportive measures, neuromuscular blocking agents or naloxone. Chest wall rigidity can last a few minutes. Duration of action 5 to 10 minutes.
Evidence	**Efficacy and safety:** **Premedication for intubation:** ***Remifentanil:*** In RCTs (LOE II): Badiee et al in 40 preterm infants undergoing the InSurE procedure compared remifentanil 2 microgram/kg over 2 minutes and atropine versus placebo and atropine. Infants who received remifentanil felt less pain but there was no difference in duration of endotracheal intubation procedure, number of attempts and oxygen desaturation between groups. Chest wall rigidity occurred in 4/20 infants and laryngospasm in 6 infants.[1]

Avino et al in 40 preterm infants undergoing elective intubation compared remifentanil 1 microgram/kg over 60 seconds and atropine versus morphine 100 microgram/kg, midazolam 50 microgram/kg and atropine. There was a similar incidence of >2 intubation attempts (4/20 vs 4/20) and no difference in intubation conditions, time or adverse events. Chest wall rigidity was reported in 2 infants receiving remifentanil.[2] Choong et al in 30 term and preterm infants undergoing elective intubation compared remifentanil 3 microgram/kg over 60 seconds and atropine versus fentanyl 2 microgram/kg over 60 seconds, succinylcholine 2 mg/kg and atropine 20 microgram/kg and reported no significant difference in time to intubation but better intubation conditions with fentanyl and succinylcholine. Chest wall rigidity was reported in 2/15 infants receiving remifentanil.[3]

Remifentanil combination: In RCTs (LOE II): Norman et al in 34 preterm infants undergoing elective intubation compared rapid sequence induction (RSI) with glycopyrrolate, thiopental 2–3 mg/kg, remifentanil 1microgram/kg (duration of administration not reported) and suxamethonium and versus atropine + morphine 0.3 mg/kg. RSI had superior intubation conditions, shorter duration of intubation and was associated with reduced duration of aEEG/EEG depression.[4, 5] Pereira e Silva et al in 20 preterm infants undergoing elective intubation compared remifentanil 1 microgram/kg and midazolam 200 microgram/kg over 60 seconds versus morphine 150 microgram/kg and midazolam 200 microgram/kg. Intubation conditions in the remifentanil group were significantly better than in the morphine group. A second intubation attempt was needed in 4 infants in the morphine group only.[6] Crawford et al in 24 infants and children undergoing elective intubation compared propofol 4.0 mg/kg and remifentanil 3 microgram/kg versus propofol 4.0 mg/kg and succinylcholine 2 mg/kg. Duration of apnoea and intubating conditions after propofol/remifentanil were similar to those after propofol/succinylcholine. Bradycardia, hypotension and chest wall rigidity did not occur.[7]
Conclusion: Remifentanil 1 to 3 microgram/kg infused over at least 60 seconds reduces but does not abolish infant pain during intubation. Studies using remifentanil as a single agent in preterm infants report chest wall rigidity in 10–20% of infants. Studies using remifentanil with another analgesic/sedative (midazolam or propofol) and/or succinylcholine have not reported chest wall rigidity as a problem. (LOE II GOR D) Further trials are required to assess the safety of remifentanil and determine the optimal intubation combination for newborn infants.

Analgesia/sedation for ventilation:
Remifentanil: In RCTs: Welzing et al in 23 term infants on mechanical ventilation compared remifentanil 0.15 microgram/kg/min adjusted in steps of 0.05 microgram/kg/min versus fentanyl 0.05 microgram/kg/min and midazolam 0.8 microgram/kg/min adjusted in steps of 0.02 microgram/kg/min. Remifentanil infusion was increased by 24% and fentanyl by 47%. Median extubation time shorter with remifentanil (80.0 versus 782.5 min, p=0.005).[8]

Remifentanil combination: In RCTs: Pereira e Silva et al in 20 preterm infants managed with mechanical ventilation and surfactant compared remifentanil 1 microgram/kg and midazolam 200 microgram/kg for intubation then remifentanil 0.5 microgram/kg/min infusion versus morphine 150 microgram/kg and midazolam 200 microgram/kg for intubation then morphine 10 microgram/kg/hour infusion. The remifentanil group had a shorter time to awaken (1173 ± 608 versus 62 ± 56.7 mins) and extubation (1320 ± 650 versus 106.3 ± 82.8 mins).[9]

Conclusion: Remifentanil 0.15 to 1 microgram/kg/min has been used for analgesia/sedation for ventilation and is associated with a shorter time to extubation than other opioids and midazolam. Chest wall rigidity has not been reported from remifentanil continuous infusion. (LOE II GOR B)

Analgesia/sedation for procedures
Laser for ROP: In RCTs: But et al in 91 preterm infants undergoing laser for ROP compared anaesthesia induced with midazolam 0.1 mg/kg and remifentanil 2 microgram/kg maintained

	with midazolam 0.1–0.2 mg/kg/hour and remifentanil 0.125–0.2 microgram/kg/min versus anaesthesia induced with 45% O_2 + 55% N_2O + 3–5% sevoflurane and fentanyl 1 microgram/kg maintained with 45% O_2 + 55% N_2O + 1–3% sevoflurane. There was no difference in complications or extubation time and mean arterial pressure values higher in remifentanil group only at 60 minutes.[10] Two case series reported analgesia/sedation with remifentanil alone or in combination in preterm infants undergoing laser for ROP. Demiel et al in 64 infants assessed remifentanil infusion 0.2 microgram/kg/min titrated up to 0.6 microgram/kg/min. Remifentanil was infused at a mean rate 0.4 ± 0.1 microgram/kg/min. No major adverse effects were observed except two patients with reversible bradycardia and hypotension. Premature infant pain profile scores revealed no pain. Extubation time was 189 ± 110 minutes.[11] Costamagna et al in 46 infants assessed propofol 3 to 4 microgram/kg bolus for intubation, then infusion of remifentanil 0.2 to 4 microgram/kg/min and propofol 2 to 20 mg/kg/hour. All the patients maintained haemodynamic stability. 21/36 patients in spontaneous ventilation before surgery were extubated within 24 hours (58.3%), 14/36 were extubated after 24 hours (38.8%) and one patient could not be extubated.[12] **Conclusion:** Remifentanil 0.2 to 0.6 microgram/kg/min has been used for analgesia/sedation for ventilated preterm infants undergoing laser for ROP and is associated with relatively short time to extubation. (LOE IV GOR C) **Insertion of PICC:** In RCTs: Lago et al in 54 preterm spontaneously breathing undergoing PICC insertion compared remifentanil 0.03 microgram/kg/min versus placebo and sucrose and non-nutritive sucking. Remifentanil reduced NIPP and PIPP scores and cardiovascular and movement response to PICC insertion but did not make the PICC easier or quicker.[13] Shin et al in 14 mechanically ventilated preterm infants compared remifentanil 0.1 microgram/kg/min versus 0.25 microgram/kg/min. There was no difference in the Premature Infant Pain Profile; there were three episodes of apnoea (42.9%) and one of bradycardia (14.3%) in the high-dose group.[14] **Conclusion:** Remifentanil 0.03 microgram/kg/min reduces pain scores and cardiovascular response to PICC insertion but may not make the PICC easier or quicker. (LOE II GOR C). **Surgery:** In RCTs: Davis et al in 60 infants undergoing pyloromyotomy compared remifentanil begun at 0.4 microgram/kg/min versus halothane expired concentration targeted 0.4% for maintenance anaesthesia. There was no difference in haemodynamic values, extubation times, discharge times, pain medications and adverse events between groups. There were no abnormal postoperative pneumograms in the remifentanil group versus three in the halothane group.[15] **Conclusion:** Remifentanil begun at 0.4 microgram/kg/min is an alternative to inhalational anaesthetic for infants undergoing surgical procedures and is not associated with adverse respiratory effects post-extubation. (LOE II GOR C) **Pharmacokinetics and pharmacodynamics:** Neonates and infants younger than 2 months of age had an enhanced clearance compared with older children indicating a high non-specific esterase activity already in very preterm infants.[16] The half-life in infants under 2 months was 5.4 ± 1.8 minutes.[17,20] Remifentanil in a bolus dose of 5 microgram/kg caused hypotension.[16, 17] **Dilution:** Drug stability data is only available for remifentanil diluted to 20 to 250 microgram/mL in a compatible fluid.[18, 19] The product excipients and drug properties of remifentanil do not suggest that the drug would be unstable at a concentration which is lower than this range. A lower final concentration of 5 microgram/mL was chosen for this formulary to aid accurate dosing and administration.
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Authors Contribution

Original author/s	David Osborn, Srinivas Bolisetty
Evidence Review	David Osborn
Expert review	
Nursing Review	Eszter Jozsa, Kirsty Minter, Priya Govindaswamy
Pharmacy Review	Michelle Jenkins, Jing Xiao, Cindy Chen
ANMF Group contributors	Nilkant Phad, Bhavesh Mehta, John Sinn, Cindy Chen, Mohammad Irfan Azeem, Michelle Jenkins, Simarjit Kaur, Joanne Malloy, Thao Tran, Helen Huynh
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty