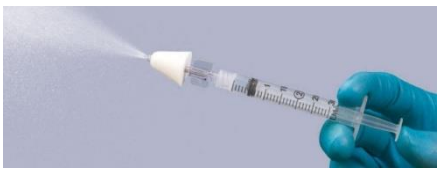
Fentanyl Intranasal
Newborn Use Only

2022

Alert	S8 High risk medication. Must be stored and handled according to local S8 drug policy. High risk of significant patient harm when used in error.
Indication	Procedural analgesia and sedation when no IV access available Comfort care
Action	Binds to specific G protein-coupled opioid receptors located in brain and spinal cord regions involved in the transmission and modulation of pain
Drug Type	Opioid analgesic agent
Trade Name	Aspen Fentanyl; DBL Fentanyl; Fentanyl GH; Fentanyl Solution (AstraZeneca); Sublimaze
Presentation	500 microgram/10 mL ampoule; 100 microgram/2 mL ampoule
Dose	1–2 microgram/kg per dose • Onset of action within 3 minutes • Duration of action 30-60 minutes[1] • Repeat after 5-10 minutes if required. Consider obtaining IV access for further analgesia.
Dose adjustment	
Maximum dose	2 doses for procedural analgesia. Additional doses may be required for comfort care.
Total cumulative dose	
Route	Intranasal
Preparation	**Infant < 3kg** Draw up 2 mL of fentanyl (100 microgram) and add 8 mL of sodium chloride 0.9% to make a final volume of 10 mL with a final concentration of 10 microgram/mL. **Infant > 3kg** Consider using undiluted Fentanyl
Administration	Dose should be given at least 5 minutes before painful procedure. Divide dose between both nostrils (maximum 0.3 mL per nostril) to optimise absorption, reduce mucosal surface saturation and runoff down the throat. **Direct administration** • Drop solution into alternating nostrils over 15 seconds **Mucosal atomisation device (MAD)** • Attach MAD to the end of a 1 mL Luer- lock syringe and prime the device with the fentanyl solution to the prescribed dose. • Insert the MAD loosely into the nostril to form a seal, preventing expulsion of fluid. • Briskly compress the syringe plunger to allow for maximal coverage of nasal mucosa with atomised particles.  
Monitoring	Hepatic and renal function with recurrent doses. Cardiorespiratory monitoring. SpO2 monitoring Urinary retention. Trauma to the nasal mucosa with recurrent doses.
Contraindications	Known hypersensitivity to fentanyl. Bilateral occluded nasal passages. Epistaxis.
Precautions	May cause respiratory depression, urinary retention and decreased intestinal motility. Reported chest wall rigidity can occur at any intravenous dose, however no reported cases with intranasal administration.
Drug Interactions	Ketoconazole and erythromycin inhibit fentanyl metabolism. When given in combination with amiodarone can cause profound bradycardia, sinus arrest and hypotension.

Adverse Reactions	Nausea and/or vomiting. Muscle/chest wall rigidity can be related to IV administration, but not reported with intranasal administration. At high doses can cause neuro-excitation and rarely seizure like activity/myoclonic movements. Respiratory depression. Bradycardia (usually atropine responsive). Urinary retention.
Compatibility	Sodium chloride 0.9%, glucose 5%
Incompatibility	Not applicable
Stability	
Storage	Store below 25°C. Protect from light. Discard remainder after use (in line with S8 drug legislation for local health district (LHD). Store in Dangerous Drug (DD) safe and record use in DD register following LHD guidance.
Excipients	Hydrochloric acid, sodium chloride, sodium hydroxide, water for injections
Special Comments	
Evidence	**Background** Fentanyl is a synthetic opioid analgesic, used in neonates because of rapid analgesia, haemodynamic stability, blocking stress responses and preventing an increase in pulmonary vascular resistance. Fentanyl is highly lipophilic, crosses the blood brain barrier rapidly, accumulates in fatty tissues and causes less histamine release than morphine. Fentanyl has greater analgesic potency, a faster onset and shorter duration of action than morphine. Intranasal fentanyl used in the prehospital and emergency department settings has been shown to be equivalent or superior to intravenous morphine in the paediatric and adult population, through a decreased time to administration as well as reduced time to achieving pain relief, with the benefit of no requirement of intravenous access.[1] Tolerance to fentanyl develops more rapidly than to morphine requiring the escalation of doses during prolonged administration.[2] **Efficacy** Several small studies have reported the effective use of intranasal (IN) fentanyl for analgesic purposes in neonates. **Analgesia** IN fentanyl dose of 2 microgram/kg/dose has been used in a 2020 double blinded randomised controlled trial conducted by Sindhur et. al., which randomised 111 neonates from 30-34 weeks corrected gestation for ROP screening. This study demonstrated pain scores (PIPP) significantly reduced in the IN fentanyl group compared to control; 8.3 vs 11.5 ($p<0.001$) with no repeat doses required.[6] A 2022 retrospective cohort study by Cheng et al. reported a reduction in PIPP (Premature Infant Pain Profile) scores in 13 preterm neonates who received intranasal fentanyl on a total of 22 occasions within a tertiary neonatal intensive care unit. IN fentanyl was given prior to administration of painful procedures, namely lumbar puncture and PICC line insertion. A mean PIPP score reduction of 1.3 (95% CI = 0.07, 2.5; p = 0.04). was observed.[4] These findings were similar to an earlier retrospective cohort study by McNair et. al., which also assessed IN fentanyl for procedural pain in 57 neonates, showing a small reduction in PIPP scores during and after the procedure (mean PIPP pain scores during and after the procedure were: 4.3 (1.8) (range 1 to 7) and 3.6 (1.5) (range 1 to 6) respectively. A repeat dose was required in 21% of patients in this study.[5] Both studies used a dosing regimen of 1-1.5 microgram/kg. **Premedication for intubation** A retrospective cohort study by Kaushal et al reviewed the use of IN fentanyl at a mean starting dose of 1.5 microgram/kg/dose (range 0.5-2.0 microgram/kg/dose) in 54 neonates who underwent a total of 61 painful procedures. A subgroup of this cohort included 40 patients who received IN fentanyl specifically for elective intubation following accidental extubation (mean dose 1.46 microgram/kg). Three repeat doses of IN fentanyl (7.5%) were required in this subgroup, as well as co-administration of IN midazolam in 48% of the total group.[7] **Palliation** Harlos et. al., retrospectively identified 11 neonates who received IN fentanyl doses between 1-2 microgram/kg for relief of agitation and respiratory distress during palliation, given that IN fentanyl has been effectively used to relieve breathlessness in adult palliative patients.[8] This study found that a dosing range of 1-1.3 microgram/kg relieved breathlessness symptoms with a mean number of three consecutive

	doses required within a 30-minute period, in order to relieve laboured breathing symptoms. Although this is the only current study reporting the use of IN fentanyl for neonatal palliative purposes, it is limited by very small patient numbers and a lack of standardisation in the reporting of neonatal dyspnoea and distress during palliation.[9] **Safety** The safety data on IN fentanyl in neonates are limited. Sindhur et al, in their RCT, noted adverse events in 4 neonates (3 in IN fentanyl group and 1 in control group). Two infants experienced desaturations while on CPAP support, which required a 5% increment in the FiO2 for a period of 10 min. Two other infants had apnea which improved with tactile stimulation and facial oxygen. All four events occurred between 3–10 min following the eye examination. Brief and self-limiting increases in oxygen requirement or changes in mechanical ventilation requirements due to desaturations were reported in cohort studies by both Kaushal and McNair.[5, 7] A systematic review identifying seven studies using IN analgosedation (fentanyl, ketamine, midazolam, dexmedetomidine) in the neonatal population, reported respiratory depression to be brief, self-limiting and responsive to tactile stimulation.[10] Chest wall rigidity requiring administration of naloxone, has not thus far been reported with IN fentanyl. Ku et al defined adverse events during the administration of IN fentanyl or midazolam to be hypotension requiring medical intervention, bradycardia, worsening respiratory status requiring intervention or escalating respiratory support and chest wall rigidity with need for neuromuscular blockade. This study found that IN fentanyl proved to be efficacious in sedation without resulting in any of these significant adverse events.[11] Administration of IN fentanyl resulting in interruption to continuous gas flow such as that provided by CPAP, as well as risk of IN fentanyl delivery causing injury to the nasal epithelium has also not yet been investigated in the literature.[10] The overall current level of safety evidence for IN fentanyl remains low due to limitations in study cohort sizes and retrospective data. **Pharmacokinetics** Fentanyl is metabolised in the liver (CYP3A4) and therefore neonatal total body clearance is low in the first days of life, particularly in the preterm population. This results in an increased risk of drug accumulation. Adult population studies have identified therapeutic levels of IN fentanyl within two minutes of administration, with a bioavailability of 89%.[12, 13] IN fentanyl is well absorbed by the nasal mucosa because it is highly lipophilic and has low molecular weight.[14] Absorption of intranasal agents is also dependent on the surface area of the nasal cavity covered by olfactory epithelium, as well as the properties of the individual drug such as its ionisation and mucociliary clearance. Drug volumes of 0.3 mL or less are more easily tolerated via the IN route in the neonatal/paediatric population, as larger volumes are prone to oropharyngeal run off causing bitter taste and burning/irritation to the nose.[10, 14] Preferred mode of delivery for IN fentanyl is through mucosal atomiser dispositive (MAD) due to increased opportunity for deposition on the ciliary surface with less oropharyngeal run off.[14] However the use of atomisers is limited by the small size of the neonatal nostril.[7] Direct delivery of IN fentanyl through rapid injection via syringe is therefore more commonly used, likely resulting in suboptimal mucosal distribution. **Summary** Intranasal fentanyl may be used as an effective agent for procedural analgesia and sedation in the neonatal population, particularly where intravenous access is limited. Doses of 1-2 microgram/kg have been reported in several small cohort studies to be efficacious without resulting in significant adverse events such as respiratory depression and chest wall rigidity. To support the routine use of IN fentanyl within NICU, larger prospective studies in the neonatal population are needed to further evaluate its safety and efficacy.
Practice points	
References	1. Borland M, Jacobs I, King B, O'Brien D. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. Annals of emergency medicine. 2007;49(3):335-40. 2. Simons SH, Anand K, editors. Pain control: opioid dosing, population kinetics and side-effects. Seminars in Fetal and Neonatal Medicine; 2006: Elsevier. 3. Bellu R, de Waal K, Zanini R. Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2010;95(4):F241-F51. 4. Cheng C, Tabbara N, Cheng C, Shah V. Intranasal Fentanyl for Procedural Analgesia in Preterm Infants. Frontiers in Pain Research. 2021;2. 5. McNair C, Graydon B, Taddio A. A cohort study of intranasal fentanyl for procedural pain management in neonates. Paediatrics & Child Health. 2018;23(8):e170-e5.

	6. Sindhur M, Balasubramanian H, Srinivasan L, Kabra NS, Agashe P, Doshi A. Intranasal fentanyl for pain management during screening for retinopathy of prematurity in preterm infants: a randomized controlled trial. Journal of Perinatology. 2020;40(6):881-7. 7. Kaushal S, Placencia JL, Maffei SR, Chumpitazi CE. Intranasal fentanyl use in neonates. Hospital Pharmacy. 2020;55(2):126-9. 8. Sitte T, Bausewein C. Intranasal fentanyl for episodic breathlessness. Journal of pain and symptom management. 2008;36(6):e3-e6. 9. Harlos MS, Stenekes S, Lambert D, Hohl C, Chochinov HM. Intranasal fentanyl in the palliative care of newborns and infants. Journal of pain and symptom management. 2013;46(2):265-74. 10. Snyers D, Tribolet S, Rigo V. Intranasal Analgosedation for Infants in the Neonatal Intensive Care Unit: A Systematic Review. Neonatology. 2022:1-12. 11. Ku L, Simmons C, Smith P, Greenberg R, Fisher K, Hornik C, et al. Intranasal midazolam and fentanyl for procedural sedation and analgesia in infants in the neonatal intensive care unit. Journal of Neonatal-Perinatal Medicine. 2019;12(2):143-8. 12. Lim S, Paech MJ, Sunderland VB, Roberts MJ, Banks SL, Rucklidge MW. Pharmacokinetics of nasal fentanyl. Journal of Pharmacy Practice and research. 2003;33(1):59-64. 13. Foster D, Upton R, Christrup L, Popper L. Pharmacokinetics and pharmacodynamics of intranasal versus intravenous fentanyl in patients with pain after oral surgery. Annals of Pharmacotherapy. 2008;42(10):1380-7. 14. Pansini V, Curatola A, Gatto A, Lazzareschi I, Ruggiero A, Chiaretti A. Intranasal drugs for analgesia and sedation in children admitted to pediatric emergency department: a narrative review. Annals of Translational Medicine. 2021;9(2). 15. Elmekkawi A, Abdelgadir D, Van Dyk J, Choudhury J, Dunn M. Use of naloxone to minimize extubation failure after premedication for INSURE procedure in preterm neonates. Journal of Neonatal-Perinatal Medicine. 2016; 9:363-70.

VERSION/NUMBER	DATE
Original 1.0	14/11/2022
Review	14/11/2027

Authors Contribution

Original author/s	Rebecca Barzegar
Evidence Review	Srinivas Bolisetty, Nilkant Phad, Bhavesh Mehta
Expert Review	Srinivas Bolisetty, Bhavesh Mehta, Karel Allegaert
Nursing Review	Eszter Jozsa, Sarah Neale
Pharmacy Review	Michelle Jenkins, Thao Tran
ANMF Group contributors	Martin Kluckow, Benjamin Emerson-Parker, Helen Huynh, Michelle Jenkins, Thao Tran, Rebecca O-Grady, Mohammad Irfan Azeem, Renee Gengaroli, Stephanie Halena
Final editing	Eszter Jozsa
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty