Fentanyl - Intravenous

Newborn use only

2023

<table>
<tr><td>Alert</td><td>S8 High risk medicine. Must be stored and handled according to local S8 drug policy
High risk of causing significant patient harm when used in error.</td></tr>
<tr><td>Indication</td><td>Analgesia.
Sedation.</td></tr>
<tr><td>Action</td><td>Binds to specific G protein-coupled opioid receptors that are located in brain and spinal cord regions involved in the transmission and modulation of pain.</td></tr>
<tr><td>Drug type</td><td>Opioid analgesic agent.</td></tr>
<tr><td>Trade name</td><td>Aspen Fentanyl; DBL Fentanyl; Fentanyl GH; Fentanyl Solution (AstraZeneca); Sublimaze</td></tr>
<tr><td>Presentation</td><td>500 microgram/10 mL ampoule; 100 microgram/2 mL ampoule</td></tr>
<tr><td>Dose</td><td>Bolus/loading dose
0.5–4 microgram/kg/dose over 3−5 minutes – may be required every 2−4 hours.

Continuous IV Infusion
1–5 microgram/kg/hour. General starting dose: 1 microgram/kg/hour. Titrate using a validated pain score.

Pre-medication for intubation
2−4 microgram/kg bolus. Wait at least 3 minutes for onset of action after giving the dose.</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia – Insufficient evidence to recommend any dose adjustment.(22, 25)
ECMO - Higher doses may be needed for procedural analgesia (23,25)
Hepatic impairment - May not need any change (24)
Renal impairment - May not need any change (21)</td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV</td></tr>
<tr><td>Preparation</td><td>SINGLE STRENGTH continuous IV infusion
<table><tr><th>Infusion strength</th><th>Prescribed amount</th></tr><tr><td>1 mL/hour = 5 microgram/kg/hour</td><td>250 microgram/kg fentanyl and make up to 50 mL</td></tr></table>Draw up 5 mL/kg (250 microgram/kg fentanyl) and make up to 50 mL with sodium chloride 0.9% or glucose 5% or glucose 10% with a concentration of 1 mL/hour = 5 microgram/kg/hour.
IV bolus from single strength solution: 0.2 mL = 1 microgram/kg

DOUBLE STRENGTH continuous IV infusion
<table><tr><th>Infusion strength</th><th>Prescribed amount</th></tr><tr><td>1 mL/hour = 10 microgram/kg/hour</td><td>500 microgram/kg fentanyl and make up to 50 mL</td></tr></table>Draw up 10 mL/kg (500 microgram/kg fentanyl) and make up to 50 mL with sodium chloride 0.9% or glucose 5% or glucose 10% with a concentration of 1 mL/hour = 10 microgram/kg/hour.
IV bolus from double strength solution: 0.1 mL = 1 microgram/kg

IV BOLUS/LOADING DOSE
Draw up 0.4 mL (20 microgram fentanyl) and add 9.6 mL sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 2 microgram/mL.

PRE-MEDICATION FOR INTUBATION
As above for IV bolus.</td></tr>
<tr><td>Administration</td><td>Slow IV bolus over 3−5 minutes
Continuous IV infusion</td></tr>
<tr><td>Monitoring</td><td>Hepatic and renal function.
Full cardiorespiratory monitoring is required.
Monitor for urinary retention.</td></tr>
<tr><td>Contraindications</td><td>Known hypersensitivity to fentanyl.</td></tr>
<tr><td>Precautions</td><td>Tolerance can occur with use >5−7 days.
Withdrawal has been reported in patients who have received continuous infusions for >5days.
Chest wall rigidity can occur at any dose.
May cause respiratory depression.
May cause urinary retention.</td></tr>
</table>

	May decrease intestinal motility.
Drug interactions	Ketoconazole and erythromycin are potent inhibitors of 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 (usually naloxone responsive). Naloxone 20-40 micrograms/kg reversed muscle rigidity immediately allowing resuscitation in a case series of 8 patients.(11) At high doses can cause neuro-excitation and rarely seizure like activity/myoclonic movements. Respiratory depression. Bradycardia (usually atropine responsive). Urinary retention.
Compatibility	**Fluids:** Sodium chloride 0.9%, glucose 5%, glucose 10% (not tested) **Y-site** (16,17): Acetaminophen, acyclovir, alfentanil, alprostadil, amikacin, amiodarone, amphotericin B lipid complex, amphotericin B liposome, ascorbic acid, atenolol, atropine, azathioprine, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, caspofungin, cefalotin, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, ciclosporin, clindamycin, clonidine, cloxacillin, dexamethasone, dexmedetomidine, digoxin, diltiazem, dobutamine, dopamine, doxycycline, enalaprilat, epinephrine, epoeitin alfa, erythromycin lactobionate, fluconazole, fluorouracil, folic acid (sodium salt), fosphenytoin, furosemide, ganciclovir, gentamicin, glycopyrrolate, heparin, hydrocortisone sodium succinate, imipenem-cilastatin, indomethacin, insulin, labetolol, lidocaine, linezolid, lorazepam, magnesium sulfate, meropenem-vaborbactam, methylprednisolone sodium succinate, metronidazole, midazolam, milrinone, morphine sulfate, naloxone, netilmicin, nitroglycerin, nitroprusside sodium, norepinephrine, octreotide, oxacillin, pamidronate, pancuronium, papaverine, penicillin G sodium, penicillin G potassium, pentobarbital, phenobarbital, phenylephrine, piperacillin, piperacillin-tazobactam, potassium chloride, potassium acetate, propofol, propranolol, protamine, pyridoxine, ranitidine, remifentanil, rocuronium, sodium acetate, sodium bicarbonate, streptokinase, succinylcholine, thiamine, thiopental, ticarcillin, tobramycin, tolazoline, urokinase, vancomycin, vasopressin, vecuronium, verapamil. **Variable compatibility:** amphotericin B conventional colloidal, ampicillin, azithromycin, diazepam, hydralazine.
Incompatibility	Fluids: No information. Y-site (16,17): Diazoxide, pantoprazole, phenytoin, sulfamethoxazole-trimethoprim.
Stability	Protect from light.
Storage	Ampoule: Store below 25°C. Protect from light. Discard remainder after use (in line with S8 drug legislation). Store in Dangerous Drug (DD) safe and record use in DD register.
Excipients	
Special comments	
Evidence	**Background** Fentanyl is a synthetic opioid analgesic, used in neonates because of rapid analgesia, hemodynamic stability, blocking stress responses and preventing increases 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. Tolerance to fentanyl develops more rapidly than to morphine, requiring the escalation of doses during prolonged administration.(18) **Efficacy** **Analgaesia:** Opioids are to be used selectively based on clinical judgment and evaluation of pain indicators, although there are limitations to pain measurement in newborns (1) (LOE 1 GOR B). Continuous infusion of fentanyl 1.1 micrograms/kg/hour (range 0.5-2.0) in the post-operative period achieves acceptable pain control but there may be increased need for ventilator support (2) (LOE II, GOR C). **Premedication for intubation:** Combinations including fentanyl reported in several small trials (3-6) and a cohort study (7). Fentanyl 2 microgram/kg - succinylcholine 2 mg/kg - atropine 20 microgram/kg combination was reported to result in better intubation condition than remifentanil (3 microgram/kg) - atropine 20 microgram/kg in newborn infants. Chest wall rigidity was reported in both groups (3) [LOE II]. A review concluded, based on current evidence, an optimal protocol for premedication is to administer a

	vagolytic (intravenous atropine), a rapid-acting analgesic (IV fentanyl 3 µg/kg to 5 µg/kg; slow infusion) and a short-duration muscle relaxant (IV succinylcholine) (8). [LOE III-2 GOR C] **Analgaesia/sedation for mechanical ventilation:** A short course of low dose fentanyl by infusion reduces behavioural sedation scores, O2 desaturations and neuroendocrine stress responses in preterm ventilated infants (9) (LOE II, GOR B). (2)In very preterm infants on mechanical ventilation, continuous fentanyl infusion plus boluses of fentanyl reduces acute pain and increases side effects but does not reduce prolonged pain compared with boluses of fentanyl alone (10) (LOE II GOR B). **Fentanyl versus morphine conversion factor:** Exact conversion factor for converting fentanyl to morphine remains unknown with literature reporting up to 100:1 for a variety of age groups. A more conservative conversion factor of 10-20 has been found to be effective for neonates. (19,20) **Fentanyl versus morphine analgesia:** In a randomized double-blind trial, neonates were allocated to receive a continuous infusion of fentanyl (10.5 microgram/kg over a 1-hour period followed by 1.5 microgram/kg/hr) or morphine (140 microgram/kg over a 1-hour period followed by 20 microgram/kg/hr) for at least 24 hours. The analgesic effect was similar in both groups. Decreased gastrointestinal motility was less frequent in the fentanyl group (23% vs 47%, P < .01).(20) **Safety** Respiratory depression occurs when anaesthetic doses (greater than 5 microgram/kg/min) are used and may also occur unexpectedly because of redistribution. Chest wall rigidity has occurred in 4% of neonates who received doses of 2.2 to 6.5 microgram/kg, occasionally associated with laryngospasm (11) (LOE IV GOR D). This was reversible with administration of naloxone. When controlling for other variables, the cumulative fentanyl dose did not correlate with neurodevelopmental outcomes in very low birth weight infants (12) (LOE III GOR C). Tolerance may develop to analgesic doses (13). Significant withdrawal symptoms have been reported in patients treated with continuous infusion and was universal for infants receiving >2.5 mg or >9 days infusion (14). [LOE IV GOR D] **Pharmacokinetics** Fentanyl is metabolised in the liver (CYP3A4) and excreted in the urine. Half-life was 9.5 hours (range 5.7 to 12.7 hours). There is significant correlation between postnatal age and total body clearance (15). Fentanyl clearance is very low during the first days of life in very preterm infants which can lead to accumulation of the drug. Clearance increases with gestational age as well as with postnatal age. Bodyweight-based fentanyl dose needs to be reduced during the first days of life to achieve comparable exposure across all preterm infants.(26)
Practice points	
References	1. Bellu R, de Waal K, Zanini R. Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed.95:F241-51. 2. Vaughn PR, Townsend SF, Thilo EH, McKenzie S, Moreland S, Denver KK. Comparison of continuous infusion of fentanyl to bolus dosing in neonates after surgery. Journal of pediatric surgery. 1996;31:1616-23. 3. Choong K, AlFaleh K, Doucette J, Gray S, Rich B, Verhey L, Paes B. Remifentanil for endotracheal intubation in neonates: a randomised controlled trial. Archives of Disease in Childhood Fetal & Neonatal Edition. 2010;95:F80-4. 4. Dempsey EM, Al Hazzani F, Faucher D, Barrington KJ. Facilitation of neonatal endotracheal intubation with mivacurium and fentanyl in the neonatal intensive care unit. Archives of Disease in Childhood: Fetal and Neonatal Edition. 2006;91:F279-F82. 5. Feltman DM, Weiss MG, Nicoski P, Sinacore J. Rocuronium for nonemergent intubation of term and preterm infants. Journal of Perinatology. 2011;31:38-43. 6. Roberts KD, Leone TA, Edwards WH, Rich WD, Finer NN. Premedication for nonemergent neonatal intubations: a randomized, controlled trial comparing atropine and fentanyl to atropine, fentanyl, and mivacurium. Pediatrics. 2006;118:1583-91. 7. Barrington KJ, Byrne PJ. Premedication for neonatal intubation. Am J Perinatol. 1998;15:213-6. 8. Barrington KJ, Hilliard RI, Jefferies AL, Peliowski-Davidovich A, Sorokan ST, Whyte HEA, Whyte RK. Premedication for endotracheal intubation in the newborn infant. Paediatrics and Child Health. 2011;16:159-64. 9. Lago P, Benini F, Agosto C, Zacchello F. Randomised controlled trial of low dose fentanyl infusion in preterm infants with hyaline membrane disease. Archives of disease in childhood Fetal and neonatal edition. 1998;79:F194-7. 10. Ancora G, Lago P, Garetti E, Pirelli A, Merazzi D, Mastrocola M, Pierantoni L, Faldella G. Efficacy and safety of continuous infusion of fentanyl for pain control in preterm newborns on mechanical ventilation. The Journal of pediatrics. 2013;163:645-51 e1.

11. Fahnenstich H, Steffan J, Kau N, Bartmann P. Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. Critical care medicine. 2000;28:836-9.
12. Lammers EM, Johnson PN, Ernst KD, Hagemann TM, Lawrence SM, Williams PK, Anderson MP, Miller JL. Association of fentanyl with neurodevelopmental outcomes in very-low-birth-weight infants. The Annals of pharmacotherapy. 2014;48:335-42.
13. Arnold JH, Truog RD, Scavone JM, Fenton T. Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. The Journal of pediatrics. 1991;119:639-43.
14. Katz R, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. Crit Care Med. 1994;22:763-7.
15. Santeiro ML, Christie J, Stromquist C, Torres BA, Markowsky SJ. Pharmacokinetics of continuous infusion fentanyl in newborns. Journal of perinatology : official journal of the California Perinatal Association. 1997;17:135-9.
16. Micromedex solutions. Fentanyl. Accessed on 23 March 2021.
17. Australian Injectable Drugs Handbook. Fentanyl. Accessed on 23 March 2021.
18. Simons SH, Anand KJ. Pain control: opioid dosing, population kinetics and side-effects. InSeminars in Fetal and Neonatal Medicine 2006;11:260-267.
19. Czarnecki ML, Hainsworth K, Simpson PM, Arca MJ, Uhing MR, Varadarajan J, Weisman SJ. Is there an alternative to continuous opioid infusion for neonatal pain control? A preliminary report of parent/nurse-controlled analgesia in the neonatal intensive care unit. Pediatric Anesthesia. 2014 Apr;24(4):377-85.
20. Saarenmaa E, Huttunen P, Leppäluoto J, Meretoja O, Fellman V. Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: a randomized trial. The Journal of pediatrics. 1999 Feb 1;134(2):144-50.
21. Dean M. Opioids in renal failure and dialysis patients. Journal of pain and symptom management. 2004;28(5):497-504.
22. Koren G, Barker C, Goresky G, Bohn D, Kent G, Klein J, et al. The influence of hypothermia on the disposition of fentanyl—Human and animal studies. European journal of clinical pharmacology. 1987;32(4):373-6.
23. Raffaeli G, Pokorna P, Allegaert K, Mosca F, Cavallaro G, Wildschut ED, et al. Drug disposition and pharmacotherapy in neonatal ECMO: from fragmented data to integrated knowledge. Frontiers in pediatrics. 2019;7:360.
24. Soleimanpour H, Safari S, Nia KS, Sanaie S, Alavian SM. Opioid drugs in patients with liver disease: a systematic review. Hepatitis monthly. 2016;16(4).
25. Wildschut ED, van Saet A, Pokorna P, Ahsman MJ, Van den Anker JN, Tibboel D. The impact of extracorporeal life support and hypothermia on drug disposition in critically ill infants and children. Pediatric Clinics. 2012;59(5):1183-204.
26. Völler S, Flint RB, Andriessen P, Allegaert K, Zimmermann LJ, Liem KD, Koch BC, Simons SH, Knibbe CA. Rapidly maturing fentanyl clearance in preterm neonates. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2019 Nov 1;104(6):F598-603.

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