Naloxone

Newborn use only

2018

Alert	Naloxone should not be administered to babies whose mothers are known or suspected to be addicted to opioids. In such cases, an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome and seizures.
Indication	1. At birth – Reversal of respiratory depression secondary to maternal opioid administration. 2. Reversal of opioid effects (to facilitate extubation or avoid intubation, post-operative apnoea)
Action	Opioid antagonist. Little or no agonistic activity.
Drug Type	Semisynthetic opioid antagonist
Trade Name	DBL Naloxone Hydrochloride Injection; Naloxone Juno Solution for injection; Naloxone Min-I-jet Prefilled syringe; Narcan Solution for injection; Prenoxad Solution for injection.
Presentation	Ampoule and prefilled syringe contain 400 microgram/mL of naloxone hydrochloride. Also contains sodium chloride. Contains 3.54 mg (0.15 mmol) of sodium. The solution is clear and colourless. pH 3.5
Dosage / Interval	1. At birth – newborn infants with respiratory depression secondary to maternal opioid administration 100 microgram/kg. Repeat dose as required. **DO NOT USE IN INFANTS BORN TO MOTHERS SUSPECTED OR KNOWN TO BE ADDICTED TO OPIOIDS.** 2. Reversal of opioid-induced respiratory depression 10–100 microgram/kg. Repeat dose as required. **CAUTION**: **Infants on prolonged opioid infusion may develop acute withdrawal following naloxone**
Maximum daily dose	2 mg
Route	Intravenous (IV) injection preferred. IM suitable if the IV route is not available. Alternate routes: intraosseous and subcutaneous.
Preparation/Dilution	400 microgram/mL
Administration	Use undiluted. Intravenous (IV) bolus at proximal cannula site. Intramuscular (IM).
Monitoring	Continuous cardiorespiratory monitoring is required. Resuscitation facilities must be readily available.
Contraindications	Naloxone is contraindicated in persons known to be hypersensitive to it.
Precautions	Naloxone should not be administered to babies whose mothers are known or suspected to be addicted to opioids. The duration of action of naloxone is short, particularly after intravenous administration, and subsequent observation of the infant should be instituted.
Drug Interactions	Naloxone reverses the analgesic and other effects of opioid agonists.
Adverse Reactions	Naloxone administered to babies whose mothers are known or suspected to be addicted to opioids may precipitate an acute withdrawal syndrome (tachycardia, tachypnoea, hypertension, tremors, vomiting and seizures). Cardiac arrest – there is a case report of a preterm neonate who developed cardiac arrest. [18]
Compatibility	Fluids: Glucose 5%, sodium chloride 0.9% Y-site: Defibrotide, linezolid
Incompatibility	Do not mix in an alkaline solution. Fluids: No information Drugs: Solutions that contain bisulfites or sulfites , calcium folinate
Stability	Infusion solution: Use within 24 hours.
Storage	Ampoule and Min-I-Jet syringe: Store below 25°C. Protect from light. Do not freeze.
Special Comments	Always establish and maintain adequate respiration before administration of naloxone to a newborn infant. The majority of infants born following intrapartum maternal opioid administration do not require administration of an opioid antagonist.

	Opioid antagonists should not be used as a substitute for provision of usual methods of clinical care and resuscitation of the newly born infant.
Evidence summary	**Efficacy:** Pediatric Advanced Life Support Guidelines [1] and Cardiac arrest in special circumstances Guidelines [2]: Naloxone reverses the respiratory depression of opioid overdose, but in persons with long-term addictions or cardiovascular disease, naloxone may markedly increase heart rate and blood pressure and cause acute pulmonary oedema, cardiac arrhythmias (including asystole) and seizures. Ventilation before administration of naloxone appears to reduce these adverse effects. Intramuscular administration of naloxone may lower the risk by slowing the onset of drug effect. The use of naloxone can prevent the need for intubation. Titrate dose until the patient is breathing adequately and has protective airway reflexes. All patients treated with naloxone must be monitored. **Opioid-exposed newborn infants with respiratory maladaptation to birth:** Systematic review [3] reported 9 trials (316 infants) that compared the effects of naloxone versus placebo. The dose of naloxone used ranged from 0.01 to 0.07 mg/kg with the exception of one study [4] in which a total dose of 0.2 mg IMI was given. None of these trials specifically recruited infants with cardiorespiratory or neurological depression. The main outcomes reported were measures of respiratory function in the first six hours of life. There is some evidence that naloxone increases alveolar ventilation. The trials did not assess the effect on admission to a neonatal unit and failure to establish breastfeeding. The existing evidence from randomised controlled trials is insufficient to determine whether naloxone confers any important benefits to newborn infants with cardiorespiratory or neurological depression that may be due to intrauterine exposure to opioid. (LOE I GOR D) **Reversal of opioid effect to facilitate extubation:** A single case series reported the outcomes of 31 infants with a mean birth weight of 1178 grams and mean gestational age 28.4 weeks who were intubated after IV atropine 0.02 mg/kg, fentanyl 3 micrograms/kg and succinylcholine 2 mg/kg for surfactant administration. Infants with an adequate respiratory drive were immediately extubated while those with apnoea or hypopnoeaa received naloxone 0.1 mg/kg/dose, repeated if needed. Twelve of thirteen (92%) infants in the naloxone group were extubated within 30 minutes of surfactant administration while 12/18 (67%) in the non-naloxone group were extubated within the same time frame. No adverse reactions were noted.[4] Conclusion: Naloxone may be effective in reversing the respiratory depression from opioid administration and facilitate extubation in preterm infants intubated for the InSurE procedure. Clinical trials are required to confirm this finding and its safety. (LOE IV GOR D). **Reduction of side effects of opioids:** There are no trials in newborns specifically for this indication. There are case reports of response to naloxone in newborn infants with morphine-induced muscle rigidity and hypoxaemia during mechanical ventilation. [6, 7] In an RCT, low dose naloxone infusion 0.25 microgram/kg/hour did not decrease fentanyl requirements in critically ill, mechanically ventilated children aged 1 day to 18 years. [8] In 23 children aged 5 months to 18 years in intensive care receiving opioid therapy, enteral naloxone for treating constipation increased stool output but induced withdrawal symptoms. [9] Conclusion: There is no role for naloxone for reducing the side effects of opioids in newborn infants. (GOR B – evidence for harm) **Post-operative apnoeas in preterm infants:** The combined effect of anaesthetics and prematurity, each of which itself results in raised endorphin activity, may result in apnoeas in preterm infants in the perioperative period. Naloxone at a dose of 5–10 microgram/kg has been used to reverse respiratory effects of anaesthetics and narcotics in the post-operative period.[14–16] **Safety:** There are few data regarding adverse effects of naloxone in newborn infants. There is concern regarding precipitating opioid withdrawal in patients with prolonged opioid exposure.[1, 2] Naloxone should not be administered to babies whose mothers are known or suspected to be addicted to opioids. In such cases, an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.[3,17] There is a case report of a preterm neonate who developed cardiac arrest following treatment with naloxone (dose 100 mcg/kg) for a ten-fold morphine overdose.[18]

	Pharmacokinetics/pharmacodynamics: In newborns, after intravenous administration of 35 (n = 6) and 70 (n = 6) micrograms of naloxone, peak levels of 4 to 15 ng/mL and 9 to 20 ng/mL respectively were reached in 5 to 40 min and the mean plasma half-life after both doses was 3.1 ± 0.5 hours. Peak levels of 7 to 35 ng/ml were reached 0.5 to 2 hour after intramuscular administration of 200 microgram (n = 17). The fall in concentration after this was consistently biphasic with the levels declining rapidly between one and four hours and then slowly from four hours onwards. Plasma concentrations at 24–36 hours after IM administration were as high as they were 4 hours after IV administration of 35 microgram which may account for the prolonged duration of action when this route is used. [10] In 26 infants born to mothers who received pethidine, naloxone was not observed to have any agonist activity, but the recommended IV dose (0.01 mg/kg) had only a slight and delayed antagonist action as measured by respiratory function tests. A more rapid and improved antagonism was noted after this dose was doubled (0.02 mg/kg). The plasma elimination-phase half-life of naloxone after intravenous cord injection was about 3 hours. [11]
References	1. Part 12: Pediatric Advanced Life Support: Web-based Integrated 2010 & 2015 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. https://eccguidelines.heart.org/index.php/circulation/cpr-ecc-guidelines-2/part-12-pediatric-advanced-life-support/?strue=1&id=3-6-6-1. 2015. 2. Truhlar A, Deakin CD, Soar J, Khalifa GE, Alfonzo A, Bierens JJ, Brattebo G, Brugger H, Dunning J, Hunyadi-Anticevic S, Koster RW, Lockey DJ, Lott C, Paal P, Perkins GD, Sandroni C, Thies KC, Zideman DA, Nolan JP, Cardiac arrest in special circumstances section C. European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances. Resuscitation. 2015;95:148-201. 3. Moe-Byrne T, Brown JV, McGuire W. Naloxone for opiate-exposed newborn infants. Cochrane Database Syst Rev. 2013:CD003483. 4. 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 5. Wiener PC, Hogg MI, Rosen M. Effects of naloxone on pethidine-induced neonatal depression. Part II--Intramuscular naloxone. Br Med J. 1977;2:229-31. 6. Van Der Lee R, Ceelie I, Tibboel D, De Wildt SN. Muscle rigidity and respiratory compromise in a term neonate during morphine infusion; serious adverse event determined by using the naranjo algorithm. Clinical Pharmacology and Therapeutics. 2009;1):S69-S70. 7. Barr PA. Hypoxaemia during mechanical ventilation for severe hyaline membrane disease following sedation with morphine sulphate. Australian Paediatric Journal. 1981;17:296-7. 8. Darnell CM, Thompson J, Stromberg D, Roy L, Sheeran P. Effect of low-dose naloxone infusion on fentanyl requirements in critically ill children. Pediatrics. 2008;121:e1363-71. 9. Tofil NM, Benner KW, Faro SJ, Winkler MK. The use of enteral naloxone to treat opioid-induced constipation in a pediatric intensive care unit. Pediatr Crit Care Med. 2006;7:252-4. 10. Moreland TA, Brice JE, Walker CH, Parija AC. Naloxone pharmacokinetics in the newborn. Br J Clin Pharmacol. 1980;9:609-12. 11. Bonta BW, Gagliardi JV, Williams V, Warshaw JB. Naloxone reversal of mild neurobehavioral depression in normal newborn infants after routine obstetric analgesia. Journal of Pediatrics. 1979;94:102-5. 12. Australian Injectable Drugs Handbook, 7th Edition. Accessed 29/08/2018: https://aidh.hcn.com.au/ 13. MIMSOnline. Accessed 29/08/2018: https://www.mimsonline.com.au.acs.hcn.com.au/ 14. Fischer CG, Cook DR. The respiratory and narcotic antagonistic effects of naloxone in infants. Anesthesia & Analgesia. 1974 Nov 1;53(6):849-52. 15. Gerhardt T, Bancalari E, Cohen H, Rocha LF. Use of naloxone to reverse narcotic respiratory depression in the newborn infant. The Journal of pediatrics. 1977 Jun 1;90(6):1009-12. 16. Beilin B, Vatashsky E, Aronson HB, Weinstock M. Naloxone reversal of postoperative apnea in a premature infant. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1985 Sep 1;63(3):317-8.

	17. Gibbs J, Newson T, Williams J, Davidson DC. Naloxone hazard in infant of opioid abuser. The Lancet. 1989 Jul 15;334(8655):159-60. 18. Deshpande G, Gill A. Cardiac arrest following naloxone in an extremely preterm neonate. European journal of pediatrics. 2009 Jan 1;168(1):115.

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