Morphine 10mg/mL (Parenteral) 2021

Newborn use only

<table>
<tr><td>Alert</td><td>S8 - High risk medication- may cause significant patient harm when used in error.</td></tr>
<tr><td>Indication</td><td>Analgesia / sedation:
1. Pre-medication prior to intubation or other procedure
2. During assisted ventilation
3. Procedures and post-surgery
4. Neonatal abstinence syndrome secondary to opioid withdrawal</td></tr>
<tr><td>Action</td><td>mu-opioid analgesic – stimulates brain opioid receptors.</td></tr>
<tr><td>Drug Type</td><td>mu-opioid analgesic.</td></tr>
<tr><td>Trade Name</td><td>DBL Morphine Sulfate (also contains sodium chloride and hydrochloric acid).
Juno Morphine Hydrochloride</td></tr>
<tr><td>Presentation</td><td>10 mg/mL (10,000 microgram/mL) ampoule</td></tr>
<tr><td>Dosage</td><td>ANALGESIA
CONTINUOUS IV INFUSION
Range: 5–40 microgram/kg/hour:
Ventilated infants or after surgery*[1,2,3]
<table>
<tr><td>Postnatal age#</td><td>Starting dose</td><td>Range</td></tr>
<tr><td>0-7 days</td><td>10 microgram/kg/hour</td><td>5-40 microgram/kg/hour</td></tr>
<tr><td>8-30 days</td><td>15 microgram/kg/hour</td><td>5-40 microgram/kg/hour</td></tr>
<tr><td>31-90 days</td><td>20 microgram/kg/hour</td><td>5-40 microgram/kg/hour</td></tr>
</table>
*Infants after cardiovascular surgery may need lower starting dose and titrated to clinical response.[2]

IV BOLUS FOR ANALGESIA
50 microgram/kg (maximum recommended 100 microgram/kg) every 4 hours.[4]

PRE-MEDICATION FOR INTUBATION
100 microgram/kg/dose (up to 200 microgram/kg) [5]

NEONATAL ABSTINENCE SYNDROME –INITIAL TREATMENT
10 microgram/kg/hour titrated to Neonatal Abstinence Syndrome scores.</td></tr>
<tr><td>Maximum Daily Dose</td><td>Doses up to 100 microgram/kg/hour have been used in newborns; however this was associated with an increase in the duration of mechanical ventilation.</td></tr>
<tr><td>Route</td><td>IV</td></tr>
<tr><td>Preparation</td><td>2-STEP DILUTION (consider for weight <2 kg)
IV Infusion: SINGLE STRENGTH
<table>
<tr><th>Prescribed amount</th><th>Infusion rate</th></tr>
<tr><td>1 mg/kg morphine and make up to 50 mL</td><td>1 mL/hour = 20 microgram/kg/hour</td></tr>
</table>
<u>Step 1:</u> Draw up 1 mL (10mg morphine in 1mL) and add 9 mL sodium chloride 0.9% to make a volume of 10 mL with a concentration of 1000 microgram/mL.
<u>Step 2</u>: From the above solution, draw up 1 mL/kg (1000 microgram/kg) and further dilute with glucose 5% or glucose 10% or sodium chloride 0.9% to make a final volume of 50 mL with a concentration of 1 mL/hour = 20 microgram/kg/hour.
IV bolus dose from single strength solution: 2.5 mL =50 microgram/kg.

IV infusion: DOUBLE STRENGTH
<table>
<tr><th>Prescribed amount</th><th>Infusion rate</th></tr>
<tr><td>2 mg/kg morphine and make up to 50 mL</td><td>1 mL/hour = 40 microgram/kg/hour</td></tr>
</table>
<u>Step 1:</u> Draw up 1 mL (10mg morphine in 1mL) and add 9 mL sodium chloride 0.9% to make a volume of 10 mL with a concentration of 1000 microgram/mL.</td></tr>
</table>

<table>
<tr><td></td><td>
<u>Step 2</u>: From the above solution, draw up 2 mL/kg (2000 microgram/kg) and further dilute with glucose 5% or glucose 10% or sodium chloride 0.9% to make a final volume of 50 mL with a concentration of 1 mL/hour = 40 microgram/kg/hour.
IV bolus dose from double strength solution: 1.25 mL =50 microgram/kg.

IV BOLUS and PRE-MEDICATION FOR INTUBATION
Draw up 1 mL (10mg morphine in 1mL) and add 9 mL sodium chloride 0.9% to make a final volume of 10mL with a concentration of 1000 microgram/mL.

<h2>1-STEP DILUTION (consider for weight 2 kg and over)</h2>
IV Infusion: SINGLE STRENGTH
<table>
<tr><th>Prescribed amount</th><th>Infusion rate</th></tr>
<tr><td>1 mg/kg morphine and make up to 50 mL</td><td>1 mL/hour = 20 microgram/kg/hour</td></tr>
</table>
Draw up 0.1 mL/kg (10mg morphine in 1mL) and add glucose 5% or glucose 10% or sodium chloride 0.9% to make a final volume of 50 mL with a concentration of 1 mL/hour = 20 microgram/kg/hour.
For IV bolus dose from single strength solution: 2.5 mL = 50 microgram/kg.

IV Infusion: DOUBLE STRENGTH
<table>
<tr><th>Prescribed amount</th><th>Infusion rate</th></tr>
<tr><td>2 mg/kg morphine and make up to 50 mL</td><td>1 mL/hour = 40 microgram/kg/hour</td></tr>
</table>
Draw up 0.2 mL/kg (10mg morphine in 1mL) and add glucose 5% or glucose 10% or sodium chloride 0.9% to make a final volume of 50 mL with a concentration of 1 mL/hour = 40 microgram/kg/hour.
For IV bolus dose from double strength solution: 1.25 mL = 50 microgram/kg.

IV BOLUS and PRE-MEDICATION FOR INTUBATION
Draw up 0.5 mL (5 mg morphine) and add 9.5 mL sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 500 microgram/mL.
</td></tr>
<tr><td>Administration</td><td>
CONTINUOUS IV INFUSION: Via syringe driver.

IV BOLUS: Administer over 5 minutes. Flush with 1 mL sodium chloride 0.9% before and after injection. Rapid IV administration may increase adverse effects.

PRE-MEDICATION FOR INTUBATION: As above for IV bolus. Wait a minimum of 5 minutes for onset of action; however for maximum effect wait 15 minutes after giving the dose.
</td></tr>
<tr><td>Monitoring</td><td>
All patients should have cardiorespiratory monitoring and be carefully observed, particularly if they are breathing spontaneously. Respiratory depression/apnoea can be reversed with naloxone.
Naloxone is contraindicated in opioid dependent infants.
Observe for urinary retention, abdominal distension or delay in passage of stool.
Withdraw slowly following prolonged use.
</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to morphine or any excipients.</td></tr>
<tr><td>Precautions</td><td>
Potentially toxic serum concentrations of morphine may occur in infants with hypoxic ischaemic encephalopathy with moderate hypothermia and infusion rates >10 microgram/kg per hour. [3] Use with caution in patients with hypersensitivity reactions to other opioids.
Hypotension and bradycardia. Respiratory depression.
Transient hypertonia. Convulsions.
Ileus and delayed gastric emptying time. Urinary retention. Renal or hepatic impairment.
Tolerance may develop after prolonged use − wean slowly.
</td></tr>
</table>

Drug Interactions	Concomitant use with other CNS depressants potentiates effects of opioids, increasing risk of respiratory depression, profound sedation or coma.
Adverse Reactions	Morphine has been associated with respiratory depression (levels above 20 ng/mL); decreased gastrointestinal motility, hypotension at higher doses, and urinary retention [4].
Compatibility	Compatibility is likely to be similar for morphine hydrochloride and sulfate. **Fluids :** **Morphine hydrochloride** – glucose 5%, sodium chloride 0.9% **Morphine sulfate** – glucose 2.5%, 5% and 10%, glucose in sodium chloride solutions, Hartmann's, sodium chloride 0.45% and 0.9% **Y-site :** **Morphine hydrochloride** – some information is available. Consult the pharmacist, pharmacy department or medicines information service for more advice. **Morphine sulfate** – adrenaline hydrochloride, amifostine, amikacin, amiodarone, ampicillin, anidulafungin, atracurium, atropine, aztreonam, bivalirudin, caspofungin, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cisatracurium, clindamycin, dexamethasone, digoxin, dopamine, eptifibatide, erythromycin, esmolol, filgrastim, fluconazole, foscarnet, gentamicin, granisetron, haloperidol lactate (in glucose), heparin sodium, hyoscine hydrobromide, insulin (short-acting), ketorolac, labetalol, lignocaine, linezolid, magnesium sulfate, methylprednisolone sodium succinate, metoclopramide, metoprolol, metronidazole, midazolam, milrinone, noradrenaline, palonosetron, paracetamol, piperacillin-tazobactam (EDTA-free), posaconazole, potassium chloride, remifentanil, sodium nitroprusside, tacrolimus, tigecycline, tirofiban, tobramycin, trimethoprim-sulfamethoxazole, vancomycin, vecuronium, zidovudine.
Incompatibility	**Fluids:** Morphine may precipitate out of solution when the final pH is greater than 6.4. **Drugs :** **Morphine hydrochloride** – esomeprazole **Morphine sulfate** – Aminophylline, azathioprine, azithromycin, flucloxacillin, folic acid, ganciclovir, indometacin, pentamidine, pethidine, promethazine, sodium nitrite, thiopental sodium.
Stability	Diluted solution for continuous IV infusion is stable for 48 hours.
Storage	Ampoule: Store below 25°C. Protect from light. Discard remainder after use (in line with schedule 8 drug legislation). Store in Dangerous Drug (DD) safe and record use in DD register.
Special Comments	Prolonged use (> 5–7 days) may be associated with dependence. Morphine hydrochloride and sulfate contain approximately equivalent amounts of morphine base per milligram.
Evidence	**Efficacy:** **Premedication:** Morphine 0.2 mg/kg bolus did not reduce the occurrence of severe hypoxia with bradycardia during intubation, in comparison with placebo.[5] [LOE II] Morphine 0.1 mg/kg – atropine 10 microgram/kg and suxamethonium 1 mg/kg premedication reduced the total time and number of attempts taken to achieve successful nasotracheal intubation of neonates compared to awake intubation;[6] [LOE II] Morphine 0.1 mg/kg – atropine 10 microgram/kg and suxamethonium 2 mg/kg was less effective than propofol with longer time to intubation, increased oxygen desaturations and nasal trauma and increased time to recovery [7]. (LOE II) No difference in time, number of attempts and duration of intubation has been reported in trials comparing morphine-midazolam versus remifentanil with or without midazolam combination [8, 9]. (LOE II) Conclusion: Morphine appears not to reduce the occurrence of severe hypoxia with bradycardia during intubation, in comparison with placebo, probably because of the delayed onset of action. It is likely that fentanyl is more effective because of the more rapid onset of action [10]. **Infants on mechanical ventilation:** A systematic review of 13 RCTs, 1505 infants, found infants given opioids showed reduced Premature Infant Pain Profile scores (MD -1.71, 95% CI -3.18 to -0.24); had no difference in mortality, incidence of hypotension, duration of mechanical ventilation and long-term and short-term neurodevelopmental outcomes; but a longer duration to reach full enteral feeding [11]. One RCT reported an increased incidence of hypotension in ventilated very

	preterm infants after morphine 100-300 micrograms/kg loading dose and with 10-30 microgram/kg/hour infusion for 24 hours [12]. Two other RCTs using morphine 50-100 micrograms/kg loading dose and with or without 10 microgram/kg/hour infusion reported no effect on blood pressure [13, 14]. One study that compared morphine with midazolam showed similar pain scores, but fewer adverse effects with morphine [15]. Conclusion: There is insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns. Opioids should be used selectively, when indicated by clinical judgment and evaluation of pain indicators. If sedation is required, morphine is safer than midazolam [11]. (LOE I GOR B) **Analgaesia:** Recommended procedural analgesic doses for neonates are: ***Intermittent Dose*** - Morphine sulfate 0.05-0.1 mg/kg intravenously; ***Infusion Dose*** **-** 0.01-0.03 mg/kg per hour. It is advised that neonatal intensive care units use only 1 opioid analgesic agent to ensure familiarity with its use. The opioid doses are only applicable for opioid-naive patients. All patients should be monitored and carefully observed, particularly if they are breathing spontaneously. Consider slow intravenous opioid infusion (morphine sulfate or fentanyl citrate) for: central venous line placement, endotracheal intubation and suction; chest tube insertion and for ventilated infants. [Consensus statement for the International Evidence-Based Group for Neonatal Pain] [4]. **Postoperative pain relief:** Continuous and intermittent morphine infusions have been trialled in postoperative patients. A continuous morphine 10 microgram/kg per hour or intermittent morphine 30 microgram/kg per 3 hours were equally effective and safe in neonates. (LOE II] A morphine continuous infusion to a targeted morphine concentration of 20 ng/ml provided more reliable analgesia than an intermittent bolus doses as needed. The average infusion rate was 20.6 ± 8.7 microgram/kg/hour. [16]. [LOE II] Postoperative morphine use can be reduced by paracetamol infusion [17]. [LOE II] **Neonatal abstinence syndrome secondary to opioids:** There are no trials of intravenous morphine for NAS secondary to opioids although its use has been reported including for seizure control [18, 19]. [LOE IV] Recommended oral dose for initial treatment of NAS in opioid dependent infants 0.5 mg/kg/day [20]. Estimated oral morphine bioavailability 48.5% in neonates [21]. (LOE IV GOR C) **Pharmacodynamics / Pharmacokinetics:** Effective morphine concentrations in the range of 10–20 ng/L have been reported [1, 22]. Concentrations above 20 ng/L have been associated with respiratory depression [2]. The mean morphine half-life is age related, reported as around 9 hours in ventilated preterm infants [23, 24], 6 hours in term infants [24, 25] and 2 hours for infants beyond 11 days age [24]. Pharmacodynamic assessment found median (IQR) average morphine infusion rate for pain relief in was 4.4 (4.0-4.8) microgram/kg/hour in postoperative term neonates <10 days versus 14.4 (11.3-23.4) microgram/kg/hour in older infants (p < 0.001) [26]. Also in postoperative term infants, morphine concentrations suggested neonates <7 days require significantly less morphine postoperatively than older neonates. The recommended dosage for continuous morphine infusions were 7 microgram/kg/h in full-term neonates; 10 microgram/kg/hour in infants >4 weeks of age [27]. (LOE II GOR B) Lynn et al estimated morphine infusion rates to achieve a steady-state concentration ≤20 ng/mL for non-cardiovascular surgery are: 0-7 days: 10 microgram/kg/hour; 8-30 days: 15 microgram/kg/hour; 31-90 days: 20 microgram/kg/hour [1]. For infants after cardiovascular surgery clearance was reduced with the following modelled rates: 0-7 days: 5 microgram/kg/hour; 8-30 days: 5 microgram/kg/hour; 31-90 days: 10 microgram/kg/hour [2].[LOE II GOR B] More restricted dosing recommendations have been suggested in neonates targeting morphine concentrations of ≤10 microgram/L [26, 27]. Infants with hypoxic ischemic encephalopathy have reduced morphine clearance and elevated serum morphine concentrations when morphine infusion rates are based on clinical state. Potentially toxic serum concentrations of morphine may occur with moderate hypothermia and infusion rates >10 microgram/kg per hour [3]. **Safety** There is no compelling evidence to support severe long-term harm, but subtler behavioural changes have been noted. Morphine use should continue to be based on clinical judgment, carefully weighing the benefits of acute interventions against the potential for long-term harm.[28]

References	1. Lynn A, Nespeca MK, Bratton SL, Strauss SG, Shen DD. Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. Anesth Analg. 1998;86:958-63. 2. Lynn AM, Nespeca MK, Opheim KE, Slattery JT. Respiratory effects of intravenous morphine infusions in neonates, infants, and children after cardiac surgery. Anesth Analg. 1993;77:695-701. 3. Roka A, Melinda KT, Vasarhelyi B, Machay T, Azzopardi D, Szabo M. Elevated morphine concentrations in neonates treated with morphine and prolonged hypothermia for hypoxic ischemic encephalopathy. Pediatrics. 2008;121:e844-9. 4. Anand KJ, International Evidence-Based Group for Neonatal P. Consensus statement for the prevention and management of pain in the newborn. Arch Pediatr Adolesc Med. 2001;155:173-80. 5. Lemyre B, Doucette J, Kalyn A, Gray S, Marrin ML. Morphine for elective endotracheal intubation in neonates: a randomized trial [ISRCTN43546373]. BMC Pediatr. 2004;4:20. 6. Oei J, Hari R, Butha T, Lui K. Facilitation of neonatal nasotracheal intubation with premedication: a randomized controlled trial. J Paediatr Child Health. 2002;38:146-50. 7. Ghanta S, Abdel-Latif ME, Lui K, Ravindranathan H, Awad J, Oei J. Propofol compared with the morphine, atropine, and suxamethonium regimen as induction agents for neonatal endotracheal intubation: a randomized, controlled trial. Pediatrics. 2007;119:e1248-55. 8. Avino D, Zhang WH, De Ville A, Johansson AB. Remifentanil versus morphine-midazolam premedication on the quality of endotracheal intubation in neonates: a noninferiority randomized trial. J Pediatr. 2014;164:1032-7. 9. Pereira e Silva Y, Gomez RS, Marcatto Jde O, Maximo TA, Barbosa RF, Simoes e Silva AC. Morphine versus remifentanil for intubating preterm neonates. Arch Dis Child Fetal Neonatal Ed. 2007;92:F293-4. 10. Barrington K. Premedication for endotracheal intubation in the newborn infant. Paediatr Child Health. 2011;16:159-71. 11. 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. 2010;95:F241-51. 12. Anand KJ, Hall RW, Desai N, Shephard B, Bergqvist LL, Young TE, Boyle EM, Carbajal R, Bhutani VK, Moore MB, Kronsberg SS, Barton BA, Group NTI. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. Lancet. 2004;363:1673-82. 13. Quinn MW, Otoo F, Rushforth JA, Dean HG, Puntis JW, Wild J, Levene MI. Effect of morphine and pancuronium on the stress response in ventilated preterm infants. Early Hum Dev. 1992;30:241-8. 14. Simons SH, Roofthooft DW, van Dijk M, van Lingen RA, Duivenvoorden HJ, van den Anker JN, Tibboel D. Morphine in ventilated neonates: its effects on arterial blood pressure. Arch Dis Child Fetal Neonatal Ed. 2006;91:F46-51. 15. Anand KJ, Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. Arch Pediatr Adolesc Med. 1999;153:331-8. 16. Lynn AM, Nespeca MK, Bratton SL, Shen DD. Intravenous morphine in postoperative infants: intermittent bolus dosing versus targeted continuous infusions. Pain. 2000;88:89-95. 17. Ceelie I, de Wildt SN, van Dijk M, van den Berg MM, van den Bosch GE, Duivenvoorden HJ, de Leeuw TG, Mathot R, Knibbe CA, Tibboel D. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. Jama. 2013;309:149-54. 18. Sarkar S, Donn SM. Management of neonatal abstinence syndrome in neonatal intensive care units: a national survey. Journal of Perinatology. 2006;26:15-7. 19. Kale-Cekinmez E, Mutlu B, Yapicioglu H, Ozlu F, Asker H, Mert K, Narli N, Satar M. Two newborns of heroin-addicted mothers suffering neonatal withdrawal syndrome. Turk J Pediatr. 2012;54:421-4. 20. National Clinical Guidelines for the Management of Drug Use during Pregnancy, Birth and the Early Development Years of the Newborn. 2006. www.health.nsw.gov.au/pubs/2006/ncg_druguse.html.

	21. Liu T, Lewis T, Gauda E, Gobburu J, Ivaturi V. Mechanistic Population Pharmacokinetics of Morphine in Neonates With Abstinence Syndrome After Oral Administration of Diluted Tincture of Opium. J Clin Pharmacol. 2016;56:1009-18. 22. Bouwmeester NJ, van den Anker JN, Hop WC, Anand KJ, Tibboel D. Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. Br J Anaesth. 2003;90:642-52. 23. Hartley R, Green M, Quinn M, Levene MI. Pharmacokinetics of morphine infusion in premature neonates. Arch Dis Child. 1993;69:55-8. 24. Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 1--Pharmacokinetics. Paediatr Anaesth. 1997;7:5-11. 25. Farrington EA, McGuinness GA, Johnson GF, Erenberg A, Leff RD. Continuous intravenous morphine infusion in postoperative newborn infants. Am J Perinatol. 1993;10:84-7. 26. Krekels EH, van Hasselt JG, Tibboel D, Danhof M, Knibbe CA. Systematic evaluation of the descriptive and predictive performance of paediatric morphine population models. Pharm Res. 2011;28:797-811. 27.Bouwmeester NJ, Hop WC, van Dijk M, Anand KJ, van den Anker JN, Tibboel D. Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. Intensive Care Med. 2003;29:2009-15. 28. Attarian S, Tran LC, Moore A, Stanton G, Meyer E, Moore RP. The neurodevelopmental impact of neonatal morphine administration. Brain sciences. 2014 Apr 25;4(2):321-34. 29. Australian Injectable Drugs Handbook, 7th Edition Online, Society of Hospital Pharmacists of Australia. Accessed via CIAP on 30/11/2018.

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Authors Contribution

Original author/s	Himanshu Popat
Review author/s	Himanshu Popat, Srinivas Bolisetty
Evidence Review	David Osborn
Nursing Review	Eszter Jozsa, Kirsty Minter
Pharmacy Review	Jing Xiao, Cindy Chen, Michelle Jenkins
ANMF Group contributors	Nilkant Phad, Thao Tran
Final content and editing review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty