# Morphine 5mg/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:<br>1. Pre-medication prior to intubation or other procedure<br>2. During assisted ventilation<br>3. Procedures and post-surgery<br>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).</td></tr>
<tr><td>Presentation</td><td>5 mg/mL (5,000 microgram/mL) ampoule</td></tr>
<tr><td>Dosage</td><td>ANALGESIA<br>CONTINUOUS IV INFUSION<br>Range: 5–40 microgram/kg/hour:<br>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>
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*Infants after cardiovascular surgery may need lower starting dose and titrated to clinical response.[2]<br><br>IV BOLUS FOR ANALGESIA<br>50 microgram/kg (maximum recommended 100 microgram/kg) every 4 hours.[4]<br><br>PRE-MEDICATION FOR INTUBATION<br>100 microgram/kg/dose (up to 200 microgram/kg) [5]<br><br>NEONATAL ABSTINENCE SYNDROME –INITIAL TREATMENT<br>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 for IV infusion (consider for weight <2 kg)<br>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 (5mg morphine in 1mL) and add 4 mL sodium chloride 0.9% to make a volume of 5 mL with a concentration of 1000 microgram/mL.<br><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.<br>IV bolus dose from single strength solution: 2.5 mL =50 microgram/kg.<br><br>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 (5mg morphine in 1mL) and add 4 mL sodium chloride 0.9% to make a volume of 5 mL with a concentration of 1000 microgram/mL.</td></tr>
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<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.<br>
IV bolus dose from double strength solution: 1.25 mL =50 microgram/kg.<br><br>
1-STEP DILUTION for IV infusion (consider for weight 2 kg and over)<br><br>
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>
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Draw up 0.2 mL/kg (5mg 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.<br>
For IV bolus dose from single strength solution: 2.5 mL = 50 microgram/kg.<br><br>
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 0.4 mL/kg (5 mg 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.<br>
For IV bolus dose from double strength solution: 1.25 mL = 50 microgram/kg.<br><br>
IV BOLUS and PRE-MEDICATION FOR INTUBATION<br>
Draw up 1 mL (5 mg morphine) and add 9 mL sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 500 microgram/mL.
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<tr><td>Administration</td><td>CONTINUOUS IV INFUSION: Via syringe driver.<br><br>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.<br><br>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.<br>Observe for urinary retention, abdominal distension or delay in passage of stool.<br>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]<br>Use with caution in patients with hypersensitivity reactions to other opioids.<br>Hypotension and bradycardia. Respiratory depression.<br>Transient hypertonia. Convulsions.<br>Ileus and delayed gastric emptying time. Urinary retention. Renal or hepatic impairment.<br>Tolerance may develop after prolonged use − wean slowly.</td></tr>
<tr><td>Drug Interactions</td><td>Concomitant use with other CNS depressants potentiates effects of opioids, increasing risk of respiratory depression, profound sedation or coma.</td></tr>
<tr><td>Adverse Reactions</td><td>Morphine has been associated with respiratory depression (levels above 20 ng/mL); decreased gastrointestinal motility, hypotension at higher doses, and urinary retention [4].</td></tr>
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| **Compatibility** | **Fluids :** glucose 2.5%, 5% and 10%, glucose in sodium chloride solutions, Hartmann's, sodium chloride 0.45% and 0.9%<br><br>**Y-site :** 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.<br><br>**Drugs :** 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.<br>Discard remainder after use (in line with schedule 8 drug legislation).<br>Store in Dangerous Drug (DD) safe and record use in DD register. |
| **Special Comments** | Prolonged use (> 5–7 days) may be associated with dependence. |
| **Evidence** | **Efficacy:**<br>**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].<br>**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)<br>**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 |

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| | 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].<br>**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]<br>**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)<br>**Pharmacodynamics / Pharmacokinetics:**<br>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].<br>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)<br>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]<br>More restricted dosing recommendations have been suggested in neonates targeting morphine concentrations of ≤10 microgram/L [26, 27].<br>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].<br>**Safety**<br>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] |
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| | 23. Hartley R, Green M, Quinn M, Levene MI. Pharmacokinetics of morphine infusion in premature neonates. Arch Dis Child. 1993;69:55-8.<br>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.<br>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.<br>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.<br>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.<br>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.<br>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**

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|---|---|
| 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, Bhavesh Mehta, John Sinn, Michelle Jenkins, Thao Tran, Helen Huynh, Simarjit Kaur, Jessica Mehegan, Joanne Malloy, Mohammad Irfan Azeem |
| Final content and editing review of the original | Ian Whyte |
| Electronic version | Cindy Chen, Ian Callander |
| Facilitator | Srinivas Bolisetty |