Morphine ORAL
Newborn Use Only

2023

Alert	S8 – High-risk medication – may cause significant patient harm when used in error. As of October 2023, Ordine ORAL solution has been discontinued in Australia. There are alternate S19A preparations accessible from 1 December 2023 through Therapeutic Goods Australia (TGA). **ANMF consensus:** The preferred S19A preparation for newborn population is Morphine sulfate -HIKMA oral solution as it doesn't contain added sugar or alcohol. **Morphine hydrochloride and morphine sulfate contain an equivalent amount of morphine base. Therefore, two preparations can be used interchangeably.**[22]
Indication	Analgesia/sedation: 1. During assisted ventilation 2. During procedures and post-surgery 3. Neonatal abstinence syndrome secondary to opioids 4. Analgesia and relief of dyspnoea including in context of palliative care
Action	Opioid analgesic − stimulates the μ-δ-opioid (Mu-Delta) receptor heteromer in the central nervous system. Modulates neurotransmitters.
Drug Type	Opioid analgesic.
Trade Name	Morphine sulfate (Hikma) – 2 mg/mL oral solution. Morphine Hydrochloride (Ordine) - 2 mg/mL and 1 mg/mL oral solution – discontinued as of Oct 2023.
Presentation	Morphine sulfate (Hikma)– Contains 2 mg/mL of morphine **SULFATE**. Morphine Hydrochloride (Ordine) – Contains 2 mg/mL or 1 mg/mL of morphine **HYDROCHLORIDE.** NOTE: Hikma brands are also available as 4mg/mL and 20mg/mL morphine sulfate products through SAS, but not approved through 19A scheme.
Dosage	**Neonatal abstinence syndrome secondary to maternal opioid dependency:** **Starting dose:** 500 microgram/kg/day divided into 4–6 equal divided doses. • Increase dose by 10−25% titrated to Neonatal Abstinence Syndrome scores (aiming for scores < 8) and clinical condition. • Decrease dose by 10–25% every 2–4 days titrated to Neonatal Abstinence Syndrome scores (when scores ≤ 4) and clinical condition. **Neonatal abstinence syndrome secondary to infant opioid infusion:** • If weaning from prolonged intravenous morphine (> 4 days), commence oral morphine using the oral:IV ratio of 2:1 (estimated oral morphine bioavailability 48.5% in neonates) [1]. So, the daily oral dose is twice the daily intravenous dose of morphine. • If weaning from intravenous fentanyl infusion, we recommend converting the total daily fentanyl dose into the equivalent intravenous morphine dose using the conversion ratio fentanyl:morphine of 1:10 (1 microgram of IV fentanyl is equivalent to 10 microgram of IV morphine) [21]. Convert the intravenous morphine dose to oral morphine dose using the ratio 1:2. That is, oral dose is twice the IV dose. **Analgesia** **Starting dose:** 50–200 microgram/kg every 3–6 hours.
Maximum Daily Dose	1.3 mg/kg/day.
Route	Oral or intragastric.
Preparation	**<u>To prepare Morphine 1 mg/mL solution</u>** **<u>Inpatients</u>** Bedside RN to prepare fresh each time. Draw up 0.5 mL of 2 mg/mL solution and add 0.5 mL of sterile water to make a final concentration of 1 mg/mL solution. Administer immediately and discard any unused portion. **<u>Outpatients</u>**

	Pharmacy can compound the solution in-house with a shelf life as per the Australian Pharmaceutical Formulary (APF) **To prepare Morphine 0.4 mg/mL solution** **Inpatients** Bedside RN to prepare fresh each time. Draw up 0.4 mL of 2 mg/mL solution and add 1.6 mL of sterile water to make a final concentration of 0.4 mg/mL solution. Administer immediately and discard any unused portion. **Outpatients** Pharmacy can compound the solution in-house with a shelf life as per the Australian Pharmaceutical Formulary (APF) **Note:** Can be administered undiluted if the strength and volume permits.
Administration	Oral. Preferably with feeds.
Monitoring	**Analgesia:** All patients should have cardiorespiratory monitoring and be carefully observed, particularly if they are breathing spontaneously. Respiratory depression/apnoea can be reversed with naloxone in opioid-naïve patients. **In infants with NAS secondary to maternal opioid dependency:** Observe for signs of respiratory and cardiac depression. Continuous cardiorespiratory monitoring is recommended if oral morphine dose is > 0.8 mg/kg/day or an additional sedative is used. Naloxone is contraindicated in opioid-dependent neonates. Respiratory depression/apnoea should be treated with supportive measures. Observe for urinary retention, abdominal distention or delay in passage of stool. Monitor Neonatal Abstinence Syndrome scores in opioid-dependent infants. Recommendations: • Commence treatment for infants with 3 scores averaging ≥ 8 or 2 scores averaging ≥ 12. • Increase treatment 10–25% if scores persistently ≥ 8 • Reduce treatment by 10–25% of the highest dose every 2–4 days if scores ≤ 4.
Contraindications	Hypersensitivity to morphine hydrochloride or any component.
Precautions	Opioid-naïve infants are at risk of cardiorespiratory depression, particularly if they are breathing spontaneously. Use with caution in patients with hypersensitivity reactions to other opioids. Hypotension and bradycardia. Transient hypertonia. Ileus and delayed gastric emptying time. Urinary retention. Tolerance may develop after prolonged use − wean slowly. Convulsions. Renal or hepatic impairment – affect metabolism and excretion.
Drug Interactions	Concomitant use with other CNS depressants potentiates effects of opioids, increasing risk of respiratory depression, profound sedation or coma.
Adverse Reactions	See Precautions.
Compatibility	N/A
Incompatibility	N/A
Stability	6 months once bottle opened.
Storage	Protect from light. Cool dry location (temp < 30°C). Store in Dangerous Drug (DD) safe and record use in DD register. Discard any diluted unused potion.
Special Comments	Prolonged use (> 5–7 days) may be associated with dependence.
Evidence	**Efficacy:** **Analgesia in opioid-naïve infants:** Oral analgesia with morphine for acute or chronic pain has not been systematically evaluated in neonates.

	Recommended analgesic doses of morphine sulfate for use in neonates are 0.05-0.1 mg/kg intravenously [3]. Estimated oral morphine bioavailability 48.5% in neonates [1]. (LOE IV GOR C) This equates to an estimated intermittent oral dose 0.1–0.2 mg/kg. Duration of analgesia 4–5 hours [4]. Intravenous morphine mean steady-state serum concentration of 15 ng/mL can be achieved in children after non-cardiac surgery in an intensive care unit with a morphine hydrochloride infusion of 7.5 microgram/kg/hour at birth (term neonates), 12.5 microgram/kg/hour at 1 month, 20 microgram/kg/hour at 3 months [5, 6]. [LOE IV] As oral morphine bioavailability in neonates averaged 48.5% [1], initial estimated daily oral morphine dose is 360 microgram/day (term infants); 600 microgram/day (at 1 month); 960 micrograms/day (at 3 months) in 4–6 equally divided doses. **Neonatal abstinence syndrome secondary to maternal opioid dependency:** Guidelines for the Management of Substance Use During Pregnancy Birth and the Postnatal Period [7]: Pharmacological treatment of infants with NAS due to opioids should be initiated when the Finnegan or modified Finnegan score averages 8 or more on 3 consecutive scores or 12 or more on 2 consecutive scores. Use of opioids for infants with NAS due to opioid withdrawal: • An opioid (morphine) should be used as initial treatment for infants with NAS due to opioid withdrawal. • Use of phenobarbitone or clonidine may reduce withdrawal severity in infants treated with an opioid. A starting dose of morphine 0.5 mg/kg/day in four divided doses (six-hourly) is recommended. Doses should be titrated to NAS scores, that is, to control infant signs of NAS [8]. It is unclear from the evidence what the starting dose of opioid should be. Most trials have commenced morphine 0.2–0.5 mg/kg per day in divided doses. Doses were titrated to NAS scores (i.e., control of infant signs) [9]. [LOE I GOR B] **Neonatal abstinence syndrome secondary to infant opioid infusion:** In neonates and infants receiving opioid infusions, high dose (fentanyl > 2.5 mg/kg) and duration of infusion (> 9 days) was predictive of withdrawal requiring treatment (NAS scores ≥ 8) [10, 11]. (LOE III-2) Infants receiving prolonged fentanyl infusions may be at higher risk of withdrawal symptoms than infants receiving prolonged morphine infusions [12]. (LOE III-2) Management of opioid withdrawal includes gradual opioid weaning, environmental and nursing supportive measures and treatment with methadone, clonidine or both [4]. **Pharmacodynamics/Pharmacokinetics:** Relative potency of morphine compared to fentanyl is 1:100 (i.e., fentanyl 0.1 mg equivalent to morphine 10 mg) in adults [2]. There is one randomised, controlled trial comparing the continuous infusion of fentanyl (10.5 microgram/kg for 1 hour followed by 1.5 microgram/kg/hour) versus morphine (140 microgram/kg for 1 hour followed by 20 microgram/kg/hour) in newborn infants undergoing mechanical ventilation which revealed equivalent analgesic effect with fewer side effects for fentanyl (21). The relative potency of fentanyl from this study in newborns compared to morphine is estimated to be 13 to 20:1 [22]. There is no study directly comparing the potency of fentanyl to morphine in newborns. (LOE II GOR B) Estimated oral morphine bioavailability 48.5% in neonates [1]. (LOE IV GOR C) In adults, morphine's elimination half-life is similar for the intravenous, intramuscular, subcutaneous and oral routes of administration [13]. Effective morphine concentrations in the range of 10–20 ng/mL have been reported [14, 15]. Concentrations above 20 nanogram/mL have been associated with respiratory depression [16]. The mean morphine half-life is age related, reported as around 9 hours in ventilated preterm infants [17, 18], 6 hours in term infants [18, 19] and 2 hours for infants beyond 11 days age [18]. Stability: Ethanol-free morphine 2 mg/mL oral solution diluted to 0.4 mg/mL with sterile water and stored in a light protected container at room temperature retained 107% of its original concentration after 60 days [20].
Practice points	

References	1. 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. 2. Anand KJ, Ingraham J. Pediatric. Tolerance, dependence, and strategies for compassionate withdrawal of analgesics and anxiolytics in the pediatric ICU. Crit Care Nurse. 1996;16:87-93. 3. 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. 4. Anand KJ, Willson DF, Berger J, Harrison R, Meert KL, Zimmerman J, Carcillo J, Newth CJ, Prodhan P, Dean JM, Nicholson C, Eunice Kennedy Shriver National Institute of Child H, Human Development Collaborative Pediatric Critical Care Research N. Tolerance and withdrawal from prolonged opioid use in critically ill children. Pediatrics. 2010;125:e1208-25. 5. Anderson BJ, Palmer GM. Recent developments in the pharmacological management of pain in children. Curr Opin Anaesthesiol. 2006;19:285-92. 6. 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. 7. NSW Health. Guidelines for the Management of Substance Use During Pregnancy Birth and the Postnatal Period. 2014. 8. 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. 9. Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database Syst Rev. 2010:CD002059. 10. Arnold JH, Truog RD, Orav EJ, Scavone JM, Hershenson MB. Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. Anesthesiology. 1990;73:1136-40. 11. 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. 12. Franck LS, Vilardi J, Durand D, Powers R. Opioid withdrawal in neonates after continuous infusions of morphine or fentanyl during extracorporeal membrane oxygenation. Am J Crit Care. 1998;7:364-9. 13. Lugo RA, Kern SE. Clinical pharmacokinetics of morphine. J Pain Palliat Care Pharmacother. 2002;16:5-18. 14. 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. 15. 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. 16. 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. 17. Hartley R, Green M, Quinn M, Levene MI. Pharmacokinetics of morphine infusion in premature neonates. Arch Dis Child. 1993;69:55-8. 18. 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. 19. 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. 20. Sauberan J, Rossi S, Kim JH. Stability of dilute oral morphine solution for neonatal abstinence syndrome. J Addict Med. 2013;7:113-5. 21. Saarenmaa E, Huttunen P, Leppaluoto J, Meretoja O, Fellman V. Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: A randomized trial. *J Pediatr.* Feb 1999;134(2):144-150. 22. Morphine Juno - Product info. Data sheet – New Zealand. Accessed on 5 October 2023. 23. Sauberan, Jason PharmD; Rossi, Steven PhD; Kim, Jae H. PhD. Stability of Dilute Oral Morphine Solution for Neonatal Abstinence Syndrome. Journal of Addiction Medicine 7(2):p 113-115, March/April 2013.

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