Midazolam
Newborn use only

2024

Alert	S4Drug – High risk medication causing significant patient harm when used in error.
Indication	Sedation during ventilation or procedure. Treatment of refractory seizure.
Action	Intensify the physiological inhibitory mechanisms mediated by gamma-aminobutyric acid (GABA) by accumulation and occupation of benzodiazepine receptors. Anti-anxiety properties are related to increasing the glycine inhibitory neurotransmitter.
Drug type	Short acting benzodiazepine.
Trade name	Hypnovel, Midazolam Alphapharm, Midazolam Pfizer, Midazolam-Baxter, B. Braun Midazolam, Midazolam Accord, Midazolam Apotex.
Presentation	5mg/mL, 5mg/5mL, 50mg/10mL, and 15mg/3mL ampoules for IV and oral use.
Dose	

Method	**Dose** [1-5]
IV infusion for sedation	0.2–1 microgram/kg/minute
IV infusion for seizures	Loading dose: 150–200 microgram/kg over 3–5 minutes Maintenance dose: 1–7 microgram/kg/minute
IV bolus	50 microgram/kg/dose every 2 hours when required. (Dose range: 50–150 microgram/kg/dose)
IM injection	50 microgram/kg/dose every 4 hours when required. (Dose range: 50–150 microgram/kg/dose)
Oral	250 microgram/kg as a single dose
Sublingual/buccal	200 microgram/kg as a single dose
Intranasal	200 microgram/kg per dose as a single dose (Dose range: 200–300 microgram/kg/dose)

Dose adjustment	Therapeutic hypothermia – No dose adjustment is required.[6] ECMO – Increased volume of distribution but reduced renal clearance and accumulation of active metabolites over time. Higher dose may be required in early stages of ECMO. Close monitoring is recommended.[7] Renal impairment – Limited data to recommend any dose adjustment. Hepatic impairment – For repeated doses and IV infusion, reduction in dosage may be required.
Maximum dose	
Total cumulative dose	
Route	IV, IM, Oral, Sublingual. Intranasal (not recommended due to nasal irritation; only under exceptional circumstances, e.g. acute refractory seizures with no alternate routes feasible).
Preparation	**IV infusion for:** **Sedation** using **5 mg/1 mL** strength

Infusion strength	Prescribed amount
1 mL/hour = 1 microgram/kg/minute	3 mg/kg midazolam and make up to 50 mL

Draw up 0.6 mL/kg (3 mg/kg of midazolam) and add glucose 5%, glucose 10%, or sodium chloride 0.9% to make final volume 50 mL. **Infusing at a rate of 1 mL/ hour = 1 microgram/kg/minute.**
IV bolus using this solution: 0.83 mL= 50 micrograms/kg

Sedation using **5mg/5 mL** strength

Infusion strength	Prescribed amount
1 mL/hour = 1 microgram/kg/minute	3 mg/kg midazolam and make up to 50 mL

Draw up 3 mL/kg (3 mg/kg of midazolam) and add glucose 5%, glucose 10%, or sodium chloride 0.9% to make final volume 50 mL. **Infusing at a rate of 1 mL/ hour = 1 microgram/kg/minute.**
IV bolus using this solution: 0.83 mL = 50 micrograms/kg

Seizures using **5 mg/1 mL** strength

	<table><tr><th>Infusion strength</th><th>Prescribed amount</th></tr><tr><td>1 mL/hour = 5 microgram/kg/minute</td><td>15 mg/kg midazolam and make up to 50mL</td></tr></table> Draw up 3 mL/kg (15 mg/kg of midazolam) and add glucose 5%, glucose 10%, or sodium chloride 0.9% to make final volume 50 mL. **Infusing at a rate of 1 mL/hour = 5 microgram/kg/minute.** **Seizures** using **5 mg/5 mL strength – Can be used for babies up to 3300 g.** <table><tr><th>Infusion strength</th><th>Prescribed amount</th></tr><tr><td>1 mL/hour = 5 microgram/kg/minute</td><td>15 mg/kg midazolam and make up to 50mL</td></tr></table> Draw up 15 mL/kg (15 mg/kg of midazolam) and add glucose 5%, glucose 10%, or sodium chloride 0.9% to make final volume 50 mL. **Infusing at a rate of 1 mL/hour = 5 microgram/kg/minute.** **IV bolus, IM, oral, sublingual** **Using 5 mg/mL ampoule** Draw up 0.4 mL (2000 microgram of midazolam) and add 9.6 mL of sodium chloride 0.9% to make final volume of 10 mL with a concentration of 200 microgram/mL. **Using 5 mg/5mL ampoule** Draw up 1 mL (1000 microgram of midazolam) and add 4 mL of sodium chloride 0.9% to make final volume of 5 mL with a concentration of 200 microgram/mL. **Intranasal** **Using 5 mg/mL ampoule** **Infant < 3kg** Draw up 0.2 mL (1000 microgram of midazolam) and add 0.8 mL of sodium chloride 0.9% to make a final volume of 1 ml and concentration of 1 mg/mL (1000 microgram/mL) Recommended maximum volume in each nostril: 0.3 mL. Larger volumes may end up in the nasopharynx.[24] **Infant ≥ 3kg** Draw up 0.4 mL (2000 microgram of midazolam) and add 0.6 mL of sodium chloride 0.9% to make a final volume of 1 ml and concentration of 2 mg/mL (=2000 microgram/mL). Recommended maximum volume in each nostril: 0.3 mL. Larger volumes may end up in the nasopharynx.[24] **Using the 5 mg/5mL ampoule** Consider using undiluted midazolam
Administration	**IV infusion:** continuous infusion via a syringe pump. Change solution every 24 hours. **IV bolus:** slow push over 10 minutes.[8] **Oral, sublingual:** Only solutions prepared from **plastic** IV ampoules may be used for oral or sublingual administration. **IM:** Inject deep into a large muscle. **Intranasal:** **Direct administration:** Drop dose into alternating nostrils over 15 seconds. Absorption is rapid; maximum effect in 10 minutes and duration up to 2 hours. May be irritating to nasal mucosa. **Mucosal atomisation device (MAD):** • Attach MAD to the end of a 1 mL Luer- lock syringe and prime the device with the midazolam solution to the prescribed dose. • Insert the MAD loosely into the nostril to form a seal, preventing expulsion of fluid. • Briskly compress the syringe plunger to allow for maximal coverage of nasal mucosa with atomised particles.
Monitoring	Apnoea, respiratory depression. Blood pressure. Level of sedation.
Contraindications	Known hypersensitivity to midazolam.
Precautions	In preterm infants, especially in extreme preterm, midazolam half-life is increased from 4–6 hours in term neonates up to 22 hours in premature infants. It is longer with impaired liver function.

	Caution when concurrently used with opioids − midazolam interacts with other central nervous system (CNS) depressants and may increase the risk of drowsiness, respiratory depression, and hypotension. Withdraw slowly after chronic administration as abrupt discontinuation may precipitate withdrawal seizures. Caution in neonates with renal and hepatic impairment − increased sensitivity to CNS effects; use doses at lower end of the range. Rapid IV infusion may result in hypotension, respiratory depression, or seizure.
Drug interactions	Concurrent administration with erythromycin promotes accumulation. Xanthines may decrease the anaesthetic/sedative effect of benzodiazepines. Care needs to be taken with adding or withdrawing caffeine or aminophylline.
Adverse reactions	Hypotension and reduced cardiac output, particularly when used in combination with fentanyl. Respiratory depression and apnoea. Hypersalivation. Nasal discomfort (with intranasal route). Seizure-like myoclonus (more common in premature neonates receiving via intravenous route).[9]
Overdose	Flumazenil is a specific benzodiazepine receptor antagonist. Dose: 10 microgram/kg IV bolus followed by repeat boluses (1-2 min) or 5 microgram/kg/min IV infusion until sedation reversed or maximum dose of 50 microgram/kg is reached.[10]
Compatibility	Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9%, and sodium chloride 0.45%. Y-site[11]: Amino acid solutions. Acetaminophen, amikacin, amiodarone, atracurium, atropine, aztreonam, calcium chloride, calcium gluconate, caspofungin, cefazolin, cefotaxime, cefoxitin, ceftriaxone, ciprofloxacin, dexmedetomidine, digoxin, diltiazem, dopamine, doxycycline, enalaprilat, epinephrine, erythromycin lactobionate, fentanyl, fluconazole, folic acid (as sodium salt), gentamicin, glycopyrrolate, heparin, isoproterenol, ketamine, labetolol, lidocaine, linezolid, lorazepam, magnesium sulfate, metronidazole, milrinone, morphine hydrochloride, morphine sulfate, multiple vitamin injection, naloxone, nitroglycerin, nitroprusside sodium, norepinephrine, octreotide, oxacillin, pamidronate, pancuronium, papaverine, penicillin G potassium, penicillin G sodium, pentoxyfylline, piperacillin, potassium chloride, procainamide, propranolol, protamine sulfate, pyridoxine, ranitidine, remifentanil, rocuronium, streptokinase, theophylline, ticarcillin, ticarcillin-clavulanate, tobramycin, urokinase, vancomycin, vasopressin, vecuronium, and verapamil. **Variable compatibility[11]:** amoxicillin-clavulanate, clindamycin, clonidine, dobutamine, furosemide, hydralazine, imipenem-cilastatin, insulin, regular, methylprednisolone sodium succinate, pantoprazole, propofol, SMOFlipid (up to 0.5 mg/mL midazolam concentration)[23], and sodium acetate.
Incompatibility	Fluids: No information. Y-site: Aciclovir, albumin, aminophylline, amoxicillin, amphotericin B cholesteryl sulfate complex, amphotericin B conventional colloidal, amphotericin B lipid complex, amphotericin B liposome, ampicillin, atenolol, azathioprine, azithromycin, cefepime, ceftazidime, chloramphenicol, cloxacillin, dexamethasone, diazepam, diazoxide, epoetin alfa, esomeprazole, flucloxacillin, fluorouracil, ganciclovir, hydrocortisone sodium succinate, ibuprofen lysine, indomethacin, omeprazole, phenobarbital (phenobarbitone), phenytoin, piperacillin-tazobactam, potassium acetate, sodium bicarbonate, sulfamethoxazole-trimethoprim, and thiopental.[11]
Stability	Diluted solution: Store at 2−8°C and use within 24 hours.
Storage	Midazolam Apotex, Midazolam-Baxter: Store below 30°C. Protect from light. B. Braun Midazolam, Hypnovel, Midazolam Alphapharm: Store below 25°C. Protect from light. Midazolam Pfizer: Store below 25°C. Protect from light. Unopened ampoules will be suitable for use for up to 8 months after the foil sachet has been opened, if protected from light. Schedule 4D (S4D) medication. Store in dangerous drug safe and record use in S4D register.
Excipients	Sodium chloride, hydrochloric acid, sodium hydroxide, and water for injections.
Special comments	Flumazenil is a specific benzodiazepine antagonist and may be used (very limited experience in the neonate) to rapidly reverse respiratory depression − 10 microgram/kg/dose IV push. May repeat every minute for up to 4 more doses.
Evidence	**Efficacy** **Sedation**

There are insufficient data to promote the use of intravenous midazolam infusion as a sedative for neonates undergoing intensive care. Although all studies included in the review reported better sedation, none of the scales used had been validated in preterm infants and thus the effectiveness could not be evaluated.[12] (Level 1, Grade B).

Intranasal midazolam for sedation: In a randomised control trial Milesi et al administered intranasal midazolam to 27 neonates of mean gestational age 27 weeks in the delivery room prior to intubation. The neonates allocated to the nasal midazolam arm received 0.1 mg/kg (0.1 mL/kg) of midazolam in each nostril. Nasal midazolam was more efficient than nasal Ketamine (89% vs 58%; p<0.01) for sedation. The haemodynamic and respiratory effects of both drugs were comparable.[4] Ku et al described a retrospective cohort of 18 infants receiving 20 intranasal doses of midazolam.[13] The median gestational age of infants at birth was 27 weeks and postnatal age was 34 days. The median dose was 0.1 mg/kg (0.1 -0.2). All the infants tolerated the medication well and none developed hypotension, bradycardia, or died.[14]

Seizures

In a small (n=39) retrospective cohort study, Conde et al reported high effectiveness of intravenous midazolam as the first line anti-seizure medication to control electrographic seizures secondary to HIE, perinatal stroke, or idiopathic in term neonates. Midazolam was administered as a 150 microgram/kg IV bolus followed by a continuous infusion 1-18 microgram/kg/min. The therapeutic response was measured as total seizure burden, maximum ictal fraction (MIF), and EEG background. Seizure activity was considered controlled if within 4 hours of reaching the maximum dose of midazolam the MIF was less than 3 minutes with > 80% reduction in average ictal fraction and there was no recurrence of EEG seizures. In 61% neonates, adequate seizure control was achieved with midazolam alone and in a further 38% neonates in combination with lidocaine. Abnormal neurodevelopment (n=10) beyond 18 months correlated with the EEG background at the beginning and 24-48 hours after seizure control but not with therapeutic response.[3]

Midazolam was effective in neonates with refractory seizures that did not respond to phenytoin or pentobarbital (pentobarbitone).[2] (Level IV, Grade D).

Intranasal midazolam for seizures: In a randomised study, Fisgin et al administered 0.2 mg/kg midazolam intranasally to 16 participants aged 0-24 months over 30 seconds using an injector. The age of youngest participants was 1 month but the number of participants of age 1 month was not clear. In 87% of the participants in the nasal midazolam group the seizures were terminated compared to 60% in the rectal diazepam group. Authors reported no major adverse events following intranasal midazolam.[5,15]

Safety

There is limited evidence of the risk/benefit ratio for sedative use in mechanically ventilated preterm neonates.

The EPIPAGE-2 cohort study reported better survival and a comparable 2-year development profile in preterm infants who received opioid and/or midazolam infusion during initial mechanical ventilation during the first week after birth. This study included infants born between completed 23- and 31-week gestation who were intubated within 1 hour of birth and remained intubated > 24 hours.

The treatment group infants (n=239) received a continuous infusion of opioids and/or midazolam during this first intubation period or day 7. The control group infants either did not receive midazolam during their stay in the NICU (n= 290) or received it after their first extubation or day 7 (n=113). The cumulative mean duration of midazolam infusion was 4 (IQR 2-11) days. Neurodevelopment was assessed in 94 infants in the treatment arm and 107 infants in the control arm.[16]

One study showed a statistically significant higher incidence of adverse neurological events (death, grade III or IV IVH, and PVL) and meta-analysis of data from two studies showed a statistically significant longer duration of NICU stay in the midazolam group compared to the placebo group.[12] (Level1, Grade B).

Administration of midazolam in ventilated premature infants causes significant changes in cerebral oxygenation and hemodynamics, which might be harmful.[17] (Level III, Grade C).

Intravenous bolus doses of midazolam in association with fentanyl should be used with great caution in the newborn, especially if very premature or with unstable blood pressure.[18] (Level IV, Grade D).

Sedation with midazolam has a transient effect on the background aEEG activity.[19] (Level III, Grade C).

Flumazenil is a specific benzodiazepine receptor antagonist. In one small, randomised control trial 40 healthy 3–12-year-old children, 500 microgram/kg oral midazolam was used for premedication and additional IV 500 microgram/kg for induction of anesthesia for circumcision surgery in addition to nitrous oxide, halothane, and bupivacaine. Reversal of sedation was attempted using a blinded study medication

	3 min after child returned to recovery after surgery. Children who received flumazenil woke up 4 times faster compared to the placebo group. The average total dose of flumazenil administered was 24(±19) microgram/kg.[10] **Pharmacokinetics** Midazolam is highly protein bound with an elimination half-life of 4−6 hours in term neonates and a variable half-life (up to 22 hours) in premature neonates and those with impaired hepatic function. Bioavailability is approximately 36% with oral administration and 50% with sublingual and intranasal administration.[20] (Level III, Grade C). Pharmacokinetic data favours low dose of IV infusion for sedation in very preterm neonates compared to more mature neonates.[1]
Practice points	
References	1. Völler S, Flint RB, Beggah F, et. Recently Registered Midazolam Doses for Preterm Neonates Do Not Lead to Equal Exposure: A Population Pharmacokinetic Model. J Clin Pharmacol. 2019 Oct;59(10):1300-1308. 2. Castro Conde JR, Hernandez Borges AA, Domenech Martinez E, et al. Midazolam in neonatal seizures with no response to phenobarbital. Neurology. Mar 8, 2005;64(5):876–879. 3. Castro Conde JR, González Campo C, et al. High Effectiveness of Midazolam and Lidocaine in the Treatment of Acute Neonatal Seizures. J Clin Neurophysiol. 2024 Jul 1;41(5):450-457. 4. Milési C, Baleine J, Mura T, et al. Nasal midazolam vs ketamine for neonatal intubation in the delivery room: a randomised trial Arch Dis Child Fetal Neonatal Ed 2018; 103: F221–F226. 5. Fişgin T, Gürer Y, Senbil N, et al. Nasal midazolam effects on childhood acute seizures. J Child Neurol. 2000 Dec; 15(12):833-5. 6. Favié, Laurent M A et al. "Phenobarbital, Midazolam Pharmacokinetics, Effectiveness, and Drug-Drug Interaction in Asphyxiated Neonates Undergoing Therapeutic Hypothermia." Neonatology vol. 116, 2 (2019): 154-162. 7. Raffaeli G, Pokorna P, Allegaert K, et al. Drug Disposition and Pharmacotherapy in Neonatal ECMO: From Fragmented Data to Integrated Knowledge. Front Pediatr. 2019; 7:360. Published 2019 Sep 3. doi:10.3389/fped.2019.00360 8. Van Den Broek MP, Van Straaten HL, Huitema AD, et al. Anticonvulsant effectiveness and hemodynamic safety of midazolam in full-term infants treated with hypothermia. Neonatology. 2015 Jan 8;107(2):150-6. 9. Gupta MK, Mondkar JA, Hegde D. Paradoxical Reaction to Midazolam in Preterm Neonates: A Case Series. Indian J Crit Care Med. 2018 Apr;22(4):300-302. 10. Jones RD, Lawson AD, Andrew LJ, et al. Antagonism of the hypnotic effect of midazolam in children: a randomized, double-blind study of placebo and flumazenil administered after midazolam-induced anaesthesia. Br J Anaesth. 1991 Jun;66(6):660-6. 11. Micromedex online. Midazolam. Accessed on 21 April 2021. 12. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD002052. 13. Ku LC, Simmons C, Smith PB, et al. Intranasal midazolam and fentanyl for procedural sedation and analgesia in infants in the neonatal intensive care unit. J Neonatal Perinatal Med. 2019;12(2):143-148. 14. Lawrence C. Ku, Catherine Simmons, Brian Smith, et al. Pediatrics Jan 2018, 141 (1 Meeting Abstract) 532; DOI: 10.1542/peds.141.1_MeetingAbstract.532. 15. Humphries LK, Eiland LS. Treatment of acute seizures: is intranasal midazolam a viable option? J Pediatr Pharmacol Ther. 2013 Apr;18(2):79-87. 16. de Tristan MA, Martin-Marchand L, Roué JM, et al. Association of Continuous Opioids and/or Midazolam During Early Mechanical Ventilation with Survival and Sensorimotor Outcomes at Age 2 Years in Premature Infants: Results from the French Prospective National EPIPAGE 2 Cohort. J Pediatr. 2021 May; 232:38-47. 17. Van Alfen-van der Velden AA, Hopman JC, Klaessens JH, Feuth T, Sengers RC, Liem KD. Effects of midazolam and morphine on cerebral oxygenation and hemodynamics in ventilated premature infants. Biology of the Neonate. 2006;90(3):197–202. 18. Burtin P, Daoud P, Jacqz-Aigrain E, Mussat P, Moriette G. Hypotension with midazolam and fentanyl in the newborn. Lancet. Jun 22, 1991;337(8756):1545–1546 19. Bernet V, Latal B, Natalucci G, Doell C, Ziegler A, Wohlrab G. Effect of sedation and analgesia on postoperative amplitude-integrated EEG in newborn cardiac patients. Pediatr Res. Jun 2010;67(6):650–655.

	20. De Wildt SN, Kearns GL, Hop WC, Murry DJ, Abdel-Rahman SM, van den Anker JN. Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. Clin Pharmacol Ther. 2001 Dec;70(6):525–31. 21. Taketomo CK, Hodding JH, Kraus DM, American Pharmacists Association. Pediatric and neonatal dosage handbook. Hudson, Ohio: Lexi-Comp: American Pharmacists Association; 2015. 22. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: Aug/15/2024). 23. Senarathna SMDKG, Strunk T, Petrovski M, Woodland S, Martinez J, Chuang VTG, Batty KT. Physical compatibility of lipid emulsions and intravenous medications used in neonatal intensive care settings. Eur J Hosp Pharm 2023; In press; doi:10.1136/ejhpharm-2023-003870. 24. Pansini V, Curatola A, Gatto A, Lazzareschi I, Ruggiero A, Chiaretti A. Intranasal drugs for analgesia and sedation in children admitted to pediatric emergency department: a narrative review. Annals of translational medicine. 2021 Jan;9(2).

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