Midazolam
Newborn use only

2021

<table>
<tr><td>Alert</td><td>S4D – High risk medication causing significant patient harm when used in error.</td></tr>
<tr><td>Indication</td><td>Sedation during ventilation or procedure.
Treatment of refractory seizure.</td></tr>
<tr><td>Action</td><td>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.</td></tr>
<tr><td>Drug type</td><td>Short acting benzodiazepine.</td></tr>
<tr><td>Trade name</td><td>Hypnovel, Midazolam Alphapharm, Midazolam Pfizer, Midazolam-Baxter, B.Braun Midazolam, Midazolam Accord, Midazolam Apotex.</td></tr>
<tr><td>Presentation</td><td>5mg/mL, 5mg/5mL, 50mg/10mL and 15mg/3mL ampoules for IV and oral use</td></tr>
<tr><td>Dose</td><td>
<table>
<tr><th>Method</th><th>Dose</th></tr>
<tr><td>IV infusion for sedation</td><td>0.2–1 microgram/kg/minute</td></tr>
<tr><td>IV infusion for seizures</td><td>Loading dose: 150–200 microgram/kg over 3–5 minutes
Maintenance dose: 1–7 microgram/kg/minute</td></tr>
<tr><td>IV bolus</td><td>50 microgram/kg/dose every 2 hours when required
(Dose range: 50–150 microgram/kg/dose)</td></tr>
<tr><td>IM injection</td><td>50 microgram/kg/dose every 4 hours when required
(Dose range: 50–150 microgram/kg/dose)</td></tr>
<tr><td>Oral</td><td>250 microgram/kg as a single dose</td></tr>
<tr><td>Sublingual</td><td>200 microgram/kg as a single dose</td></tr>
<tr><td>Intranasal</td><td>200 microgram/kg per dose as a single dose
(Dose range: 200–300 microgram/kg/dose)</td></tr>
</table>
</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia – No dose adjustment is required.(17)
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.(16)
Renal impairment – Limited data to recommend any dose adjustment.
Hepatic impairment – For repeated doses and IV infusion, reduction in dosage may be required.</td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>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).</td></tr>
<tr><td>Preparation</td><td>IV
Sedation using 5 mg/1 mL strength

<table>
<tr><th>Infusion strength</th><th>Prescribed amount</th></tr>
<tr><td>1 mL/hour = 1 microgram/kg/minute</td><td>3 mg/kg midazolam and make up to 50 mL</td></tr>
</table>
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. Infuse at a rate of 1 mL/ hour = 1 microgram/kg/minute.

Sedation using 5mg/5 mL strength

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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. Infuse at a rate of 1 mL/ hour = 1 microgram/kg/minute.

Seizures using 5 mg/1 mL strength

<table>
<tr><th>Infusion strength</th><th>Prescribed amount</th></tr>
</table>
</td></tr>
</table>

	<table><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. **Infuse at a rate of 1 mL/hour = 5 microgram/kg/minute.** **Seizures** using **5 mg/5 mL strength (not to be used for babies over 3.3 Kg)** <table><tr><td>Infusion strength</td><td>Prescribed amount</td></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. **Infuse at a rate of 1 mL/hour = 5 microgram/kg/minute.** **IV bolus, IM, oral, sublingual and intranasal** 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.
Administration	IV infusion: continuous infusion via a syringe pump. Change solution every 24 hours. IV bolus: slow push over 10 minutes.[9] Oral, sublingual: Plastic IV ampoules may be used for oral or sublingual administration. Intranasal: IV ampoules may be used for intranasal 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. IM: Inject deep into a large muscle.
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 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 central nervous system (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).
Compatibility	Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9%, sodium chloride 0.45%. Y-site (10,11): 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, verapamil. **Variable compatibility (10,11):** amoxicillin-clavulanate, clindamycin, clonidine, dobutamine, furosemide, hydralazine, imipenem-cilastatin, insulin, regular, methylprednisolone sodium succinate, pantoprazole, propofol, sodium acetate.
Incompatibility	Fluids: No information. Y-site (10,11): Fat emulsion. 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, thiopental.
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, 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** 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 [1] (Level 1, Grade B). Midazolam was effective in neonates with refractory seizures that did not respond to phenobarbital (phenobarbitone), phenytoin or pentobarbital (pentobarbitone) [2] (Level IV, Grade D). 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 0.1mg/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 (12). Ku et al described a retrospective cohort of 18 infants receiving 20 intranasal doses of Midazolam. 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 (13). 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 (14,15). **Safety** One study showed a statistically significant higher incidence of adverse neurological events (death, grade III or IV IVH, 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 [1] (Level1, Grade B). Administration of midazolam in ventilated premature infants causes significant changes in cerebral oxygenation and hemodynamics, which might be harmful [3] (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 [4] (Level IV, Grade D). Sedation with midazolam has a transient effect on the background aEEG activity [5] (Level III, Grade C). **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 [6] (Level III, Grade C).
Practice points	
References	1. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. The Cochrane database of systematic reviews. 2012;6:CD002052. 2. Castro Conde JR, Hernandez Borges AA, Domenech Martinez E, Gonzalez Campo C, Perera Soler R. Midazolam in neonatal seizures with no response to phenobarbital. Neurology. Mar 8 2005;64(5):876–879. 3. 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. 4. 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 5. 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. 6. 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. 7. Taketomo CK, Hodding JH, Kraus DM, American Pharmacists Association. Pediatric and neonatal dosage handbook. Hudson, Ohio: Lexi-Comp: American Pharmacists Association; 2015. 8. Australian Injectable Drugs Handbook, 6th Edition, Society of Hospital Pharmacists of Australia 2014. 9. Van Den Broek MP, Van Straaten HL, Huitema AD, Egberts T, Toet MC, De Vries LS, Rademaker K, Groenendaal F. Anticonvulsant effectiveness and hemodynamic safety of midazolam in full-term infants treated with hypothermia. Neonatology. 2015 Jan 8;107(2):150-6. 10. Micromedex online. Midazolam. Accessed on 21 April 2021. 11. Australian injectable drugs handbook. Midazolam. Accessed on 22 April 2021. 12. 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. 13. 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. 14. Fişgin T, Gürer Y, Senbil N, et al. Nasal midazolam effects on childhood acute seizures. J Child Neurol. 2000 Dec; 15(12):833-5. 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. 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. 17. 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. 18.

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