High Alert

midazolam (mid-**ay**-zoe-lam)

~~Versed~~

Classification

Therapeutic: antianxiety agents, sedative/hypnotics
Pharmacologic: benzodiazepines

Schedule IV

Pregnancy Category D

Indications

PO: Preprocedural sedation and anxiolysis in pediatric patients. **IM, IV:** Preoperative sedation/anxiolysis/amnesia. **IV:** Provides sedation/anxiolysis/amnesia during therapeutic, diagnostic, or radiographic procedures (conscious sedation): Aids in the induction of anesthesia and as part of balanced anesthesia, As a continuous infusion, provides sedation of mechanically ventilated patients during anesthesia or in a critical care setting, Status epilepticus.

Action

Acts at many levels of the CNS to produce generalized CNS depression. Effects may be mediated by GABA, an inhibitory neurotransmitter. **Therapeutic Effects:** Short-term sedation. Postoperative amnesia.

Pharmacokinetics

Absorption: Rapidly absorbed following oral and nasal administration; undergoes substantial intestinal and first-pass hepatic metabolism. Well absorbed following IM administration; IV administration results in complete bioavailability.

Distribution: Crosses the blood-brain barrier and placenta; excreted in breast milk.

Protein Binding: 97%.

Metabolism and Excretion: Almost exclusively metabolized by the liver, resulting in conversion to hydroxymidazolam, an active metabolite, and 2 other inactive metabolites (metabolized by cytochrome P450 3A4 enzyme system); metabolites are excreted in urine.

Half-life: Preterm neonates: 2.6–17.7 hr; Neonates: 4–12 hr; Children: 3–7 hr; Adults: 2–6 hr (increased in renal impairment, HF, or cirrhosis).

TIME/ACTION PROFILE (sedation)

ROUTE	ONSET	PEAK	DURATION
IN	5 min	10 min	30–60 min
IM	15 min	30–60 min	2–6 hr
IV	1.5–5 min	rapid	2–6 hr

Contraindications/Precautions

Contraindicated in: Hypersensitivity; Cross-sensitivity with other benzodiazepines may occur; Shock; Comatose patients or those with pre-existing CNS depression; Uncontrolled severe pain; Acute angle-closure glaucoma; ***OB:*** Benzodiazepine drugs may ↑ risk of congenital malformations; use in the last weeks of pregnancy has caused CNS depression in the neonate; ***Lactation:*** Lactation; ***Pedi:*** Products containing benzyl alcohol should not be used in neonates.

Use Cautiously in: Pulmonary disease; HF; Renal impairment; Severe hepatic impairment; Obese pediatric patients (calculate dose on the basis of ideal body weight); ***Pedi:*** Rapid injection in neonates has caused severe hypotension and seizures, especially when used with fentanyl; ***Geri:*** Older patients (especially >70 yr) are more susceptible to cardiorespiratory depressant effects; dosage ↓ required.

Adverse Reactions/Side Effects

CNS: agitation, drowsiness, excess sedation, headache. **EENT:** blurred vision. **Resp:** APNEA, LARYNGOSPASM, RESPIRATORY DEPRESSION, bronchospasm, coughing. **CV:** CARDIAC ARREST, arrhythmias. **GI:** hiccups, nausea, vomiting. **Derm:** rashes. **Local:** phlebitis at IV site, pain at IM site.

Interactions

Drug-Drug: ↑ CNS depression with **alcohol**, **antihistamines**, **opioid analgesics**, and other **sedative/hypnotics** (↓ midazolam dose by 30–50% if used concurrently). ↑ risk of hypotension with **antihypertensives**, **opioid analgesics**, acute ingestion of **alcohol**, or **nitrates**. Midazolam is metabolized by the cytochrome P450 3A4 enzyme system; drugs that induce or inhibit this system may be expected to alter the effects of midazolam. **Carbamazepine**, **phenytoin**, **rifampin**, **rifabutin**, and **phenobarbital** ↓ levels. **Erythromycin**, **cimetidine**, **ranitidine**, **diltiazem**, **verapamil**, **fluconazole**, **itraconazole**, and **ketoconazole** ↓ metabolism and may ↑ risk of toxicity.

Drug-Natural Products: Concomitant use of **kava-kava**, **valerian**, or **chamomile** can ↑ CNS depression. Long term use of **St. John's wort** may significantly ↓ levels.
Drug-Food: Grapefruit juice ↓ metabolism and may ↑ risk of toxicity.

Route/Dosage

Dose must be individualized, taking caution to reduce dose in geriatric patients and in those who are already sedated.

Preoperative Sedation/Anxiolysis/Amnesia

PO (Children 6 mo–16 yr): 0.25–0.5 mg/kg, may require up to 1 mg/kg (dose should not exceed 20 mg); *patients with cardiac/respiratory compromise or concurrent CNS depressants*—0.25 mg/kg.
IM (Adults Otherwise Healthy and <60 yr): 0.07–0.08 mg/kg 1 hr before surgery (usual dose 5 mg).
IM (Adults ≥60 yr, Debilitated or Chronically Ill): 0.02–0.03 mg/kg 1 hr before surgery (usual dose 1–3 mg).
IM (Children): 0.1–0.15 mg/kg up to 0.5 mg/kg 30–60 min prior to procedure; not to exceed 10 mg/dose.

Conscious Sedation for Short Procedures

IV (Adults and Children Otherwise Healthy >12 yr and <60 yr): 1–2.5 mg initially; dosage may be ↑ further as needed. Total doses >5 m g are rarely needed (↓ dose by 50% if other CNS depressants are used). Maintenance doses of 25% of the dose required for initial sedation may be given as necessary.
IV (Children 6–12 yr): 0.025–0.05 mg/kg initially, then titrate dose carefully, may need up to 0.4 mg/kg total, maximum dose 10 mg.
IV (Children 6 mo–5 yr): 0.05 mg/kg initially, then titrate dose carefully, may need up to 0.6 mg/kg total, maximum dose 6 mg.
IV (Geriatric Patients ≥60 yr, Debilitated or Chronically Ill): 1–1.5 mg initially; dose may be ↑ further as needed. Total doses >3.5 m g are rarely needed (↓ dose by 30% if other CNS depressants are used). Maintenance doses of 25% of the dose required for initial sedation may be given as necessary.
Intranasal (Children): 0.2–0.3 mg/kg, may repeat in 5–15 min.

Status Epilepticus

IV (Children >2 mo): 0.15 mg/kg load followed by a continuous infusion of 1 mcg/kg/min. Titrate dose upward q 5 min until seizure controlled, range: 1–18 mcg/kg/min.

Induction of Anesthesia (Adjunct)

May give additional dose of 25% of initial dose if needed.
IV (Adults Otherwise Healthy and <55 yr): 300–350 mcg/kg initially (up to 600 mcg/kg total). If patient is premedicated, initial dose should be further ↓.
IV (Geriatric Patients >55 yr): 150–300 mcg/kg as initial dose. If patient is premedicated, initial dose should be further ↓.
IV (Adults —Debilitated): 150–250 mcg/kg initial dose. If patient is premedicated, initial dose should be further ↓.

Sedation in Critical Care Settings

IV (Adults): 0.01–0.05 mg/kg (0.5–4 mg in most adults) initially if a loading dose is required; may repeat q 10–15 min until desired effect is obtained; may be followed by infusion at 0.02–0.1 mg/kg/hr (1–7 mg/hr in most adults).
IV (Children): *Intubated patients only*—0.05–0.2 mg/kg initially as a loading dose; follow with infusion at 0.06–0.12 mg/kg/hr (1–2 mcg/kg/min), titrate to effect, range: 0.4–6 mcg/kg/min.
IV (Neonates >32 wk): *Intubated patients only*—0.06 mg/kg/hr (1 mcg/kg/min).
IV (Neonates <32 wk): *Intubated patients only*—0.03 mg/kg/hr (0.5 mcg/kg/min).

NURSING IMPLICATIONS

Assessment

- Assess level of sedation and level of consciousness throughout and for 2–6 hr following administration.
- **Monitor BP, pulse, and respiration continuously during IV administration. Oxygen and resuscitative equipment should be immediately available.**
- ***Toxicity and Overdose:*** If overdose occurs, monitor pulse, respiration, and BP continuously. Maintain patent airway and assist ventilation as needed. If hypotension occurs, treatment includes IV fluids, repositioning, and vasopressors.
- The effects of midazolam can be reversed with flumazenil (Romazicon).

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Potential Nursing Diagnoses

Ineffective breathing pattern (Adverse Reactions)
Risk for injury (Side Effects)

Implementation

- ***High Alert:*** Accidental overdose of oral midazolam syrup in children has resulted in serious harm or death. Do not accept orders prescribed by volume (5 mL or 1 tsp); instead, request dose be expressed in milligrams. Have second practitioner independently check original order and dose calculations. Midazolam syrup should only be administered by health care professionals authorized to administer conscious sedation.
- **PO:** To use the *Press-in Bottle Adaptor (PIBA),* remove the cap and push bottle adaptor into neck of bottle. Close bottle tightly with cap. Solution is a clear red to purplish-red cherry-flavored syrup. Then remove cap and insert tip of oral dispenser in bottle adaptor. Push the plunger completely down toward tip of oral dispenser and insert firmly into bottle adaptor. Turn entire unit (bottle and oral dispenser) upside down. Pull plunger out slowly until desired amount of medication is withdrawn into oral dispenser. Turn entire unit right side up and slowly remove oral dispenser from the bottle. Tip of dispenser may be covered with tip of cap until time of use. Close bottle with cap after each use.
- Dispense directly into mouth. Do not mix with any liquid prior to dispensing.
- **Intranasal:** Administer using a 1 mL needleless syringe into the nares over 15 sec. Using the 5 mg/mL injection, administer half dose into each nare.
- **IM:** Administer IM doses deep into muscle mass, maximum concentration 1 mg/mL.

IV Administration

- **pH:** 2.9–3.7.
- **Direct IV:** ***Diluent:*** Administer undiluted or diluted with D5W or 0.9% NaCl. ***Concentration:*** Undiluted: 1 mg/mL or 5 mg/mL. Diluted: 0.03–3 mg/mL. ***Rate:*** Administer slowly over at least 2–5 min. Titrate dose to patient response. Rapid injection, especially in neonates, has caused severe hypotension.
- **Continuous Infusion:** ***Diluent:*** Dilute with 0.9% NaCl or D5W. ***Concentration:*** 0.5–1 mg/mL. ***Rate:*** Based on patient's weight (see Route/Dosage section). Titrate to desired level of sedation. Assess sedation at regular intervals and adjust rate up or down by 25–50% as needed. Dose should also be decreased by 10–25% every few hours to find minimum effective infusion rate, which prevents accumulation of midazolam and provides more rapid recovery upon termination.
- **Y-Site Compatibility:** alemtuzumab, alfentanil, amikacin, amiodarone, anidulafungin, argatroban, atracurium, atropine, aztreonam, benztropine, bivalirudin, bleomycin, buprenorphine, calcium chloride, calcium gluconate, carboplatin, carmustine, caspofungin, cefazolin, cefotaxime, cefoxitin, ceftaroline, ceftriaxone, ciprofloxacin, cisatracurium, cisplatin, cyanocobalamin, cyclophosphamide, cyclosporine, cytarabine, dactinomycin, daptomycin, dexmedetomidine, digoxin, diltiazem, diphenhydramine, docetaxel, dopamine, doripenem, doxacurium, doxarubicin hydrochloride, doxycycline, enalaprilat, epinephrine, epirubicin, eptifibatide, erythromycin lactobionate, esmolol, etomidate, etoposide, etoposide phosphate, famotidine, fenoldopam, fentanyl, fluconazole, fludarabine, folic acid, gemcitabine, gentamicin, glycopyrrolate, granisetron, heparin, hydromorphone, idarubicin, ifosfamide, irinotecan, isoproterenol, labetalol, levofloxacin, lidocaine, linezolid, lorazepam, magnesium sulfate, mannitol, mechlorethamine, meperidine, metaraminol, methadone, methoxamine, methyldopate, metoclopramide, metoprolol, metronidazole, milrinone, mitoxantrone, morphine, multivitamins, mycophenolate, nalbuphine, naloxone, nesiritide, nicardipine, nitroglycerin, nitroprusside, norepinephrine, octreotide, ondansetron, oxacillin, oxaliplatin, oxytocin, paclitaxel, palonosetron, pamidronate, pancuronium, papaverine, pemetrexed, penicillin G potassium, pentamidine, pentazocine, phentolamine, phenylephrine, phytonadione, potassium chloride, procainamide, promethazine, propranolol, protamine, pyridoxime, quinupristin/dalfopristin, ranitidine, remifentanil, rifampin, rocuronium, streptokinase, succinylcholine, sufentanil, tacrolimus, teniposide, theophylline, thiotepa, tigecycline, tirofiban, tobramycin, tolazoline, trimetaphan, vancomycin, vasopressin, vecuronium, verapamil, vincristine, vinorelbine, voriconazole, zoledronic acid.
- **Y-Site Incompatibility:** acyclovir, aminocaproic acid, aminophylline, amphotericin B cholesteryl, amphotericin B colloidal, amphotericin B lipid complex, amphotericin B liposome, ampicillin, ampicillin/sulbactam, ascorbic acid, azathioprine, cefepime, ceftazidime, cefuroxime, chloramphenicol, dantrolene, dexamethasone sodium phosphate, diazepam, diazoxide, epoetin alfa, ertapenem, fluorouracil, foscarnet, fosphenytoin, furosemide, ganciclovir, indomethacin, ke-

torolac, methotrexate, micafungin, omeprazole, pantoprazole, pentobarbital, phenobarbital, phenytoin, piperacillin/tazobactam, potassium acetate, prochlorperazine, sodium bicarbonate, thiopental, trimethoprim/sulfamethoxazole.

Patient/Family Teaching

- Inform patient that this medication will decrease mental recall of the procedure.
- May cause drowsiness or dizziness. Advise patient to request assistance prior to ambulation and transfer and to avoid driving or other activities requiring alertness for 24 hr following administration.
- Instruct patient to inform health care professional prior to administration if pregnancy is suspected.
- Advise patient to avoid alcohol or other CNS depressants for 24 hr following administration of midazolam.

Evaluation/Desired Outcomes

- Sedation during and amnesia following surgical, diagnostic, and radiologic procedures.
- Sedation and amnesia for mechanically ventilated patients in a critical care setting.

Why was this drug prescribed for your patient?