Midazolam: an essential palliative care drug

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Abstract: Midazolam is a commonly used benzodiazepine in palliative care and is considered one of the four essential drugs needed for the promotion of quality care in dying patients. Acting on the benzodiazepine receptor, it promotes the action of gamma-aminobutyric acid. Gamma-aminobutyric acid action promotes sedative, anxiolytic, and anticonvulsant properties. Midazolam has a faster onset and shorter duration of action than other benzodiazepines such as diazepam and lorazepam lending itself to greater flexibility in dosing than other benzodiazepines. The kidneys excrete midazolam and its active metabolite. Metabolism occurs in the liver by the P450 system. This article examines the pharmacology, pharmacodynamics, and clinical uses of midazolam in palliative care.

Keywords: agitation, benzodiazepines, delirium, dyspnea, gamma-aminobutyric acid, imidazole ring, insomnia, midazolam, palliative sedation, seizures

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Introduction

Since the accidental synthesis of the first benzodiazepine, chlordiazepoxide, in 1961, benzodiazepines have emerged as important agents for symptom control in palliative medicine. Benzodiazepines treat a variety of symptoms in palliative care, including anxiety, delirium associated with alcohol withdrawal, seizures, and when symptoms are refractory, they are used for palliative sedation therapy. Benzodiazepines combined with haloperidol is emerging as an effective treatment for delirium. Benzodiazepines if misused can lead to withdrawal symptoms and cognitive impairment. The ideal benzodiazepine for use in palliative care would be one where there is a rapid onset of action, yet have a short duration to minimize adverse effects. Midazolam is one benzodiazepine fitting this description. This review examines the pharmacology, pharmacodynamics, and evidence for use in palliative medicine. Midazolam is considered one of the four essential drugs that should be available in all settings caring for dying patients.

Structure of midazolam

Midazolam contains a benzene ring fused to a seven-membered diazepine ring (see Figure 1).

Figure 1. Structure Midazolam.

Pharmacodynamics

Midazolam binds with high affinity to the benzodiazepine receptor, which is at the interface of the α and γ subunits of the gamma-aminobutyric acid receptor (GABA). GABA receptors mediate inhibitory functions in the human brain. They are protein complexes consisting of five subunits, arranged pseudo-symmetrically around an ion channel selective for chloride (Cl⁻). The major receptor, GABAₐ, consists of α₁, β₂, and γ₂ subunits. Benzodiazepines bind to the α and γ interface leading to anxiolytic, sedative, muscle relaxant, and anticonvulsant actions. Benzodiazepines are considered exogenous modulators of the GABA
receptor. When compared with other benzodiazepines, midazolam binds to the GABA benzodiazepine binding site as avidly as clonazepam (Ki 0.85 ± 0.02 nM) and lorazepam, but more avidly than diazepam (Ki 10 ± 1 nM).

Pharmacokinetics and metabolism
Midazolam exists in a pH equilibrium between closed and open ring structures. The benzodiazepine ring of midazolam opens at lower pH. At physiologic pH, the ring closes and the molecule becomes lipid soluble allowing rapid penetration across the blood–brain barrier. The pH characteristics of midazolam allow preparation of salts that are readily soluble in aqueous media. Midazolam onset of action is rapid regardless of the route. Both the intravenous (IV) and subcutaneous routes manifest onset of action within minutes. Following IV administration, midazolam has a distribution half-life of 6–15 min. Midazolam has an elimination half-life of 1.5–3 h. The duration of action is 60–120 min. The lipophilic nature of midazolam accounts for the relatively large volume of distribution at steady state, that is, 0.8–1.7 l/kg. Oxidation of the imidazole ring leads to greater clearance than other benzodiazepines such as diazepam. Intramuscular midazolam is rapidly absorbed with the onset of action within 2 min of administration. Peak serum concentrations occur between 23 and 40 min. Intramuscular midazolam has a bioavailability of 90%. Intranasal (IN) midazolam has a rapid onset of action with a $T_{\text{max}}$ of 10–14 min. Bioavailability ranges between 60% and 80%. Increases in $C_{\text{max}}$ and AUC are dose proportional. Oral bioavailability is 40–50% due to extensive first-pass metabolism. When given orally, the onset of action is approximately 15 min reflecting its rapid absorption from the gastrointestinal (GI) tract. CYP3A4 and CYP3A5 hydroxylate midazolam. Patients with CYP3A4 mutations can experience increased sedation. Metabolism yields three metabolites, α-hydroxy midazolam, 4-hydroxy midazolam, and α,4-dihydroxy midazolam, all excreted as glucuronides. α-hydroxy-midazolam is pharmacologically active with sedative properties like that of midazolam. It is a formation rate-limited metabolite and closely follows midazolam concentrations. When glucuronidated, the α-hydroxy metabolite loses its potency and is one-tenth as potent as midazolam. α-Hydroxy-midazolam accumulates to a greater extent after oral administration because of the first-pass metabolism. The α-hydroxy-midazolam metabolite has an elimination half-life of 1 h in humans. Excretion of midazolam is primarily by the kidneys.

### Dosing in special populations

**Liver disease**
Advanced cirrhosis reduces the plasma clearance and prolongs the half-life of midazolam. MacGilchrist and coworkers showed that cirrhotic patients had a significantly ($p < 0.05$) prolonged elimination half-life of midazolam (3.9 versus 1.6 h) compared with a control group. The cirrhotic group experienced more profound sedation for up to 6 h when compared with controls. Critically ill patients with liver failure need careful dosing of midazolam.

**Renal disease**
Midazolam accumulates and can cause prolonged sedation in patients with renal dysfunction. Patients can experience prolonged sedation in the setting of severe renal failure. The active metabolite α-hydroxymethyl midazolam accumulates and contributes to sedation. Because patients...
with chronic renal failure and hypoalbuminemia have a higher fraction of unbound drug at greater risk for adverse effects, careful dosing of continuous infusions is necessary.31

**Advanced illness**

Terminally ill patients experience significant physiologic changes affecting drug disposition. Loss of body weight and cachexia can lead to a decrease in Vd (volume of distribution). Decreasing Vd leads to increases in drug concentration and effect for lipophilic drugs like midazolam.32 Low albumin levels, commonly seen in advanced illness, decrease the clearance of midazolam.33

**Elderly**

Midazolam clearance decreases in the elderly. Prolonged elimination of half-life occurs in the elderly.34 Liver blood flow decreases with age, and midazolam is a drug with a low hepatic extraction (0.3), so elimination prolongs in low hepatic blood flow states.32,35

**Pediatric**

In healthy neonates, the half-life ($t_{1/2}$) and the clearance (Cl) are 3.3-fold longer and 3.7-fold shorter, respectively, than in adults owing to low levels of CYP3A4 and CYP3A5. These enzymes do not surge until the fourth week of life. Disease affects the pharmacokinetics of midazolam in neonates; multiple organ failure reduces the clearance of midazolam, and mechanical ventilation prolongs the $t_{1/2}$ of this drug. Extracorporeal membrane oxygenation (ECMO) therapy increases $t_{1/2}$, Cl, and Vd of midazolam several times.36 Large inter-individual variations in midazolam clearance values exist in critically ill neonates, infants, children, and adolescents.37 Midazolam appears to be a safe drug to use in neonates with incidences of hypotension and respiratory depression in low percentages.36

**Drug interactions**

CYP3A4 metabolizes midazolam almost exclusively to its hydroxyl metabolites.38 Inducers and inhibitors of CYP3A4 potentially affect midazolam levels. Drugs such as glucocorticoids, antifungals, antibiotics, retrovirals, antidepressants, calcium channel blockers, and H2 blockers interact to influence the disposition of midazolam.38,39

Table 2 summarizes the effects of midazolam drug interactions.

Specific drug interactions are noted below. In general, the combination of benzodiazepines with drugs like opioids and antihistamines increases the risk of sedation and respiratory depression.

**Adverse effects**

Besides somnolence, most adverse effects are of low frequency.68 Clinical trials show that midazolam is safe to give with opioids for the treatment of dyspnea in advanced illness.69,70 Hiccups occur with an incidence of approximately 3.6%.71 Benzodiazepines cause disinhibition reactions to occur in both adult and pediatric patients, and midazolam is no exception.72 However, benzodiazepines in combination with antipsychotics help control delirium.73 Vorsanger and Roberts reported two cases of athetoid movements after receiving midazolam as a premedication.74 Physostigmine reversed the movement. Midazolam can cause prolonged anterograde amnesia.75–77

**Clinical applications of midazolam in palliative care**

**Palliative sedation therapy**

Terminally ill cancer patients near the end of life can experience refractory symptoms, which require palliative sedation. Midazolam is the most common benzodiazepine used for palliative sedation therapy.78,79 It is also considered the first-line drug because of its ability to be easily reversed, lending itself to use in respite sedation and short-term palliative sedation.80 One report in adult palliative sedation found mean midazolam doses of 29 mg/day (median: 30 mg, range: 15–60 mg/day).81 A recent study in an Israeli hospice found average doses of midazolam up to 79 mg/day.82 Mercadante and coworkers found mean doses were 23–58 mg/day.83 Midazolam is useful for palliative sedation in the home setting for pediatric patients.84 Initial doses were in the range of 0.02–0.08 mg/kg/h.84 Mean dose was 0.02–1.0 mg/kg/h.84 In treating terminal restlessness and agitation, Bottomley and Hanks15 used continuous infusion of subcutaneous midazolam in 23 advanced cancer patients in hospice. The investigators achieved symptom control in 22 of 23 patients using initial doses of 0.4–0.8 mg/h. The mean maximum dose was 2.9 mg/h. Dosing varied between patients highlighting the need to individualize dosing.
Midazolam along with droperidol or olanzapine remains a treatment option for agitated patients in the emergency room.85

**Dyspnea**

Opioids are useful for the treatment of terminal dyspnea and anxiolytics help manage the anxiety.

| Drug                          | Effect                                                                 | Mechanism of action | Clinical importance                                |
|-------------------------------|------------------------------------------------------------------------|---------------------|---------------------------------------------------|
| Glucocorticoids               | Decreased AUC (64%) and increased clearance of midazolam (127%)40      | Induction of CYP3A  | Prednisone does not affect pharmacokinetics of midazolam41 |
| Phenytoin                     | Phenytoin lowers midazolam levels. Bioavailability may be reduced as much as 90% according to some studies62 | Induction of CYP3A4 | Unknown                                           |
| Herbal medicine St John’s wort| Increased midazolam clearance43-45                                      | Induction of CYP3A4 | Unknown                                           |
| Non-nucleoside reverse transcriptase inhibitor (efavirenz) | Oral clearance increased by 70%, and midazolam systemic clearance after intravenous administration was significantly increased by 27%46 | Induction of CYP3A4 | Unknown                                           |
| Fluconazole                   | Increase AUC and half-life of midazolam48,49                           | Inhibition of CYP3A | Unknown                                           |
| Itraconazole                  |                                                                           |                     |                                                   |
| Ketoconazole                  |                                                                           |                     |                                                   |
| Posaconazole                  |                                                                           |                     |                                                   |
| Chemotherapy agents           |                                                                           |                     |                                                   |
| Nilotinib                     | Nilotinib inhibits CYP3A450                                             | Inhibition of CYP3A4| Unknown                                           |
| Idelalisib                    | Idelalisib increases the AUC of midazolam fivefold51                   | Inhibition of CYP3A4| Unknown                                           |
| Crizotinib                    | Crizotinib inhibits CYP3A452                                            | Inhibition of CYP3A4| Unknown                                           |
| Pazopanib                     | Pazopanib only weakly inhibits CYP3A53                                  | Inhibition of CYP3A4| Unknown                                           |
| Paclitaxel                    | Midazolam may interfere with paclitaxel metabolism56 and AUC of midazolam57 | Inhibition of CYP3A4| Unknown                                           |
| Ceritinib                     |                                                                           |                     |                                                   |
| Grapefruit juice              | Delays absorption and reduces first-pass effect on midazolam resulting in increased blood plasma levels of midazolam of 56% and increased midazolam bioavailability of 35%55 | Inhibition of CYP3A4| Unknown                                           |
| Protease inhibitors           | Inhibit CYP3A4 leading to increased midazolam levels56,57              | Inhibition of CYP3A4| May prolong sedation and increase sedation risk58 |
| [ritonavir, atazanavir, darunavir, fosamprenavir] |                                                                           |                     |                                                   |
| Simeprevir [treatment of hepatitis C infection] | Increased AUC of midazolam [oral] by 1.3–1.459 | Inhibition of CYP3A4 | Unknown                                           |
| Calcium channel blockers      | Increase the AUC for midazolam60,61                                     | Inhibition of CYP3A4| Unknown                                           |
| Antidepressants               |                                                                           |                     |                                                   |
| Fluvoxamine                   | Nefazodone [now discontinued] inhibits CYP3A4 and increases the AUC by 400%62 | Inhibition of CYP3A4| No reported interaction with mirtazapine          |
| Paroxetine                    |                                                                           |                     |                                                   |
| Citalopram                    |                                                                           |                     |                                                   |
| Aprepitant                    | Increases the AUC63–66                                                  | Inhibition of CYP3A4| Especially at doses of 125 mg aprepitant63         |
| Oral midazolam                |                                                                           |                     | 125 mg aprepitant63 and 37.5 mg aprepitant63 Oral midazolam |
| Netupitant/palonosetron       | Increases $C_{max}$ by 40% and AUC increased by 144%67                 | Inhibition of CYP3A4| Unknown                                           |
| combination                   |                                                                           |                     |                                                   |

AUC, Area under the curve.
associated with dyspnea. One trial (single-blinded) studied subcutaneous midazolam as an adjunct therapy to morphine in treating severe dyspnea in terminally ill cancer patients (N=101).69 Patients received one of three treatments. The morphine group consisted of subcutaneous scheduled morphine (2.5 mg every 4 h for opioid-naïve patients or a 25% increment over the daily dose for those receiving baseline opioids) with midazolam rescue doses (5 mg) for breakthrough dyspnea. The midazolam group received scheduled midazolam (5 mg every 4 h) with morphine rescues (2.5 mg) for breakthrough dyspnea. The morphine–midazolam group received scheduled morphine (2.5 mg every 4 h for opioid-naïve patients or a 25% increment over the daily dose for those receiving baseline opioids) and midazolam (5 mg every 4 h) with morphine rescue doses (2.5 mg) for breakthrough dyspnea. 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Seizures
Midazolam, as well as diazepam and lorazepam, are drugs most widely used as initial management for status epilepticus which is defined as seizures lasting more than 5 min or more than one seizure without recovery in between.87,88 Midazolam is one of the best studied drugs in the out-of-hospital setting. The RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial) study identified intramuscular midazolam as being non-inferior to IV lorazepam in both adults and children for seizures persisting more than 5 min.89,90 Midazolam is versatile in that it controls status epilepticus by a variety of routes, including IV and subcutaneous routes. It is effective when given buccally, intranasally, or rectally.91 Potential drawbacks when using the IN route include seizing patients spitting or blowing out medication during administration.90 In the hospice setting, lorazepam or midazolam can be considered for status. Lorazepam may be favored due to its longer half-life, but as seen with the RAMPART study, both drugs are efficacious.91

Analgesic effect
Ho and Ismail analyzed 13 randomized controlled trials (RCTs) looking at the analgesic effect of intrathecal midazolam. Studies suggest a delay in need of rescue analgesia in the postoperative setting. Intrathecal midazolam did not affect motor blockade.92

Insomnia and terminal illness
Matsuo and Morita evaluated IV midazolam for insomnia in palliative care patients and found it to be as effective as flunitrazepam, but more costly.93 Incidences of a hangover effect, delirium,
treatment withdrawal, or death did not differ. Respiratory depression, defined as apnea, respiratory arrest, and decreased respiratory rate, occurred significantly more often in those receiving flunitrazepam than midazolam. Midazolam given subcutaneously works well also for insomnia in palliative care.94

**Delirium and agitation**
Goncalves and coworkers95 found the combination of intramuscular haloperidol and midazolam to control agitation in advanced cancer in 91% of cases. Agar and coworkers used midazolam as a rescue medication for refractory delirium. In that study, there were better outcomes in the placebo–midazolam rescue arm than the other arms which used antipsychotics and rescue midazolam.73

**Ketamine emergence phenomena**
Midazolam has been used to treat or prophylactically treat emergence phenomenon associated with ketamine use.96

**Hiccups**
Midazolam may be useful in the management of hiccups in terminal illness.97

**Pruritis and biliary obstruction**
Prieto found the use of continuous infusion of midazolam to be effective in refractory pruritis associated with biliary obstruction. The original intent was to use midazolam for sedation given the refractory nature of the pruritis. Surprisingly, the pruritis improved and there was minimal sedation. Midazolam was started subcutaneously at 1 mg per hour after a 2 mg bolus. The dose was increased 1 mg every 15 min as needed for itching. During the next 4 weeks, the patient was slowly titrated to 84 mg/h of midazolam, with total control of his itching.98

**Muscle spasm**
Parenteral benzodiazepines, such as midazolam, can be used to relieve muscle spasm and spasticity in the last days of life (Table 3).27

**Pediatric dosing**
Dosing in children is weight based.37 There is a fourfold variation in dosage administration (30–120 µg/kg/h) for children between the ages of 6 months and 12 years. In critically ill children, there is greater than fourfold variation in midazolam clearance. The greater variation in midazolam clearance values than the dosage schedule suggests that many children may receive too high or too low a dose of midazolam to obtain satisfactory sedation. This may explain the poor sedation achieved in clinical trials with midazolam in critically ill children. As a group, pediatric patients generally require higher dosages of midazolam hydrochloride (mg/kg) than do adults. Younger (less than 6 years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients and may require close monitoring. Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly with concomitant use of fentanyl.107 Doses given to children must be calculated on a mg/kg basis. For children 6 months to 5 years of age, a dose of 0.05–0.1 mg/kg is recommended. Dosages up to 0.6 mg/kg titrated slowly may be necessary to achieve the desired endpoint. For children 6–12 years of age, the recommended dose is 0.025–0.05 mg/kg with doses up to 0.4 mg/kg to achieve the desired endpoint.14

**Route conversions and conversions from other benzodiazepines**
Converting midazolam from the oral to IV subcutaneous route uses a 2:1 ratio.22,108 Midazolam’s potency in comparison with other benzodiazepines is shown in Table 4.27 This may be useful when switching from one benzodiazepine to another when greater clinical efficacy is required.

**Pharmacoeconomics**
The cost of giving midazolam given by IV injection/subcutaneous injection ranges from 1.75 to 8 US dollars/dose depending on concentration. This is comparable with the cost of IV Ativan.109

**Conclusion**
Midazolam is a benzodiazepine with sedative, anxiolytic, muscle relaxant, and anticonvulsant properties. Its lipid soluble properties allow rapid action. Advantages also include the ability to be given by multiple routes and its short half-life. The short half-life allows for reversibility of drug effect if desired. Clinicians should consider this drug when there is a need for a short-acting,
As a versatile drug, it is used for the management of palliative sedation, terminal restlessness, seizures, and dyspnea. It can be used to manage anxiety and symptoms of dyspnea in the setting of withdrawal of care and catastrophic bleeding. Disadvantages of the drug include propensity to be rapidly metabolized with continued use.

Table 3. Schedule of Administration.

| Indication               | Dosing                                      | Comment                                                                                     |
|--------------------------|---------------------------------------------|--------------------------------------------------------------------------------------------|
| Palliative sedation      | 1–5 mg IV bolus every 5 min until comfortable or maximum of 20 mg. Continuous infusion is started generally 0.5–1 mg/h. Usual effective dose range is 1–20 mg/h subcutaneously or intravenously. | If the continuous infusion rate reaches 20 mg/h, then some have recommended switching to another sedating agent. Can also be given subcutaneously. |
| Terminal agitation       | Wide dosing range. Usual starting dose 0.4–0.8 mg/h. Doses may go up to 3 mg/h. Patients may become tolerant to midazolam necessitating dose increase. As needed dosing can match the hourly dose and can be given as frequently as q 15 min. | If necessary, increase both the as-needed dose and the infusion until the patient is calm. Some experts recommend considering adding an antipsychotic if the dose reaches >30 mg/24 h by continuous infusion. Haloperidol is suggested as an antipsychotic. |
| Dyspnea                  | Midazolam dosing for dyspnea is up to 5 mg subcutaneously or intravenously every 4 h. Oral midazolam at 2 mg orally as often as every 4 h has been shown to be beneficial. Rescue doses at 50–100% of the scheduled dose are given as frequent as every 15 min. |                                                                                               |
| Seizures                 | Midazolam boluses of 0.1–0.3 mg/kg are used for status epilepticus. Continuous infusions of 0.05–0.4 mg/kg/h can also be used. Other dosing recommendations for seizures include 10 mg intranasally, intramuscularly, or buccally for patients with a body weight of >40 kg or 5 mg for a patient with a body weight of 13–40 kg. | It may take up to 10 min to abort the seizure; doses can be repeated if the seizure persists after 5 min. |
| Catastrophic bleeding    | 5–10 mg IV every 5 min to a maximum dose of 20 mg. |                                                                                               |
| Insomnia                 | Midazolam 2.0 mg subcutaneously/IV to maximum dose of 18 mg qhs. |                                                                                               |

Table 4. Benzodiazepine Equivalents.

| Drug     | Dose (mg) |
|----------|-----------|
| Diazepam | 5         |
| Lorazepam| 0.5       |
| Midazolam| 5         |
| Alprazolam| 0.5     |

rapid-onset benzodiazepine. As a versatile drug, it is used for the management of palliative sedation, terminal restlessness, seizures, and dyspnea. It can be used to manage anxiety and symptoms of dyspnea in the setting of withdrawal of care and catastrophic bleeding. Disadvantages of the drug include propensity to be rapidly metabolized with continued use.

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