Midazolam Subcutaneous and Nasal - Palliative Care (Adults)

Contents

1. Overview

Purpose

This protocol outlines the administration, prescribing and monitoring of subcutaneous and nasal midazolam at Te Whatu Ora - Waitematā.

Scope

All medical and nursing staff.

⚠ This guideline is for use in the palliative context of care and in patients who are approaching end of life ONLY.

2. Presentation

1. Midazolam 5mg/5ml ampoules
2. Midazolam 15mg/3ml ampoules
3. Midazolam nasal spray 5mg/ml (15ml) (manufactured by Te Whatu Ora Health New Zealand - Waitematā Inpatient Pharmacy).

Midazolam Subcutaneous and Nasal - Palliative Care (Adults)

3. Indications

3.1 Licensed

Sedation, induction and maintenance of anaesthesia.

3.2 Unlicensed

Restlessness, anxiety, respiratory distress, terminal agitation, seizures, myoclonic jerks, intractable hiccup, skeletal muscle relaxant.[2, 3]

Unlicensed route of administration

Subcutaneous.

4. Contraindications and Precautions

4.1 Contraindications

1. Patients with known hypersensitivity to midazolam or other benzodiazepines[1]
2. Unless the patient is imminently dying, avoid in:
   a. enia gravis.[2, 6]Acute or severe pulmonary insufficiency
   b. Severe respiratory depression
   c. Untreated sleep apnoea syndrome
   d. Severe liver disease
   e. Myasth

4.2 Precautions

- Chronic respiratory insufficiency
- Hepatic failure
- Impaired cardiac function
- Chronic renal failure.[1, 6]

Prescribing Midazolam - note

- There is variable sensitivity to midazolam and it is often unpredictable.
- The risk of apnoea with intravenous midazolam is high and this route is rarely used in palliative patients also because they are often on other medications, such as opioids that can also respiratory depression.

⚠ The safest and preferred route of administration is the **subcutaneous route**. When prescribing subcutaneous midazolam, consider switching concurrent medications, especially i.v. opioids to the subcutaneous route as well.

⚠ Prolonged treatment can lead to physical dependence - avoid sudden withdrawal of midazolam as it may precipitate withdrawal symptoms (e.g. anxiety, confusion, seizures, hallucinations, insomnia).[5]

Midazolam Subcutaneous and Nasal - Palliative Care (Adults)

5. Mechanism of Action

Midazolam is a short-acting benzodiazepine with GABA potentiating actions in the central nervous system (CNS).[2] It relieves anxiety, is a sedative, an anticonvulsant and a muscle relaxant.[1] It is metabolised extensively by the CYP3A4 and CYP3A5 enzymes in the liver to metabolites, of which one is possibly active. One of the metabolites can also accumulate in renal impairment, increasing risk of sedation.[3, 5]

6. Dose

6.1 Subcutaneous Midazolam

Indication	Starting and PRN doses	Initial Infusion Rate via CSCI* over 24 hours	Dose Range per 24 hours
Anxiety **Restlessness** **Respiratory distress/agitation** **Muscle tension/spasm** **Multifocal myoclonus** **Intractable hiccup**	2.5 mg subcutaneously (subcut) STAT then 2.5mg to 5 mg subcut every 30 minutes PRN (use 1.25mg subcut in cachectic, frail/elderly patients – can be repeated q15mins PRN)	10mg	10 – 30 mg[1] higher doses may be used (up to 60 mg/24 hours)
Seizures	5mg subcut STAT then 5mg subcut every 5 minutes PRN	15 - 30mg	30 – 60mg
Prevention of benzodiazepine withdrawal in patients no longer able to swallow oral medications	2.5mg to 5 mg subcut STAT then 2.5mg to 5mg subcut every 30 minutes PRN	10 mg	

**CSCI – Continuous subcutaneous infusion*

Note:
1) There is no maximum dose for midazolam however the dose should be titrated carefully according to the response. *Seek advice from the Palliative care team if dose in excess of 30mg / 24 hours is required.*
2) Consider administering an anti-psychotic (e.g. haloperidol) prior to or in conjunction with midazolam if confusion, hallucinations or other psychoses accompanies restlessness and agitation. Refer to *Delirium Assessment – Palliative Care* and *Delirium Management – Palliative Care*.

⚠ Consider dose reduction in liver impairment and those with creatinine clearance <10ml/min due to increased risk of sedation as a result of active metabolite accumulation.[5]

6.2 Midazolam Nasal Spray

The main indication for midazolam nasal spray is anxiety associated with breathlessness. For more information on dyspnoea in Palliative Care, refer to *Dyspnoea (breathlessness) Assessment – Palliative Care* and *Dyspnoea (breathlessness) Management – Palliative Care.*

There is no commercial preparation of midazolam nasal spray available in New Zealand. It must be compounded for each patient by the pharmacy. The amount delivered by each spray depends on the spray bottle used. The spray bottles used at Te Whatu Ora Health New Zealand - Waitematā dispense 0.1ml of solution = 0.5mg of midazolam per spray. The spray may also be administered via the buccal route.

The dose required is patient and indication dependant. Prescribe as **'1 spray into each nostril q1h PRN'.**

Midazolam Subcutaneous and Nasal - Palliative Care (Adults)

6.3 Converting to subcutaneous midazolam

Midazolam is the preferred benzodiazepine for subcutaneous use. Compared to the other benzodiazepines, it has the shortest half-life (see section 6.4), making it easy to adjust dose to effect. It also has good documented compatibility with most other commonly used medications in the palliative care setting (section 7.3). Therefore, patients on other benzodiazepines should be converted to subcutaneous midazolam using the table below which shows the 24hr dose of other benzodiazepines equivalent to 2.5mg of regular subcutaneous midazolam /24hours. Remember to also prescribe PRN midazolam for breakthrough symptoms.

Subcut Midazolam Dose Equivalencies of Commonly Used Benzodiazepines		
Benzodiazepine	**Total dose (last 24 hours) and Route**	**Equivalence**
Diazepam	10mg PO/PR	2.5mg subcut midazolam
Clonazepam	1mg PO/SC	
Lorazepam	1mg PO/IV	
Oxazepam	15 to 30mg PO	
Temazepam	10mg PO	
Midazolam Spray	5 nasal sprays (=2.5mg)	

Example: A patient is on 1 mg lorazepam PO (equivalent to 2.5 mg subcut midazolam) and used 7 nasal sprays of midazolam in the last 24 hours (equivalent to 3.5 mg subcut midazolam). This is equivalent to a total dose of subcut midazolam of 6 mg/24hrs. Round *down* to 5 mg midazolam via CSCI over 24 hours. Chart 2.5mg q4hrly subcut PRN.

6.4 Half-lives of commonly used benzodiazepines

Drug	Half life
Diazepam	25 – 50 hrs
Clonazepam	20 – 60 hrs
Lorazepam	10 – 20 hrs
Oxazepam	6 – 20 hrs
Temazepam	8 – 15 hrs
Midazolam	1.5 – 2.5 hrs

*Information from Palliative Care Formulary 6th edition.

7. Administration

Diluent

- For subcutaneous bolus administration, midazolam does not need to be diluted.
- When added to a syringe driver the recommended diluent is water for injection.[2]

Additional Equipment

- Subcutaneous Saf-T-Intima single lumen [ADM140] (*refer to Subcutaneous Site Selection, Insertion and Monitoring of BD Saf-T-Intima Cannula*).
- Continuous subcutaneous infusion pump (Niki T34) if required.

Midazolam Subcutaneous and Nasal - Palliative Care (Adults)

7.1 Compatibility

Compatible with:

Water for injection, 0.9% sodium chloride, morphine sulfate, morphine tartrate, haloperidol, hyoscine hydrobromide, metoclopramide, ketamine, methadone, fentanyl, oxycodone, levomepromazine, hyoscine butylbromide, octreotide, ondansetron, tramadol.[2, 3, 4, 5]

7.2 Incompatible with (concentration dependent):

Cyclizine, Dexamethasone[4, 5]

⚠ Do not use if the solution is cloudy or a precipitate is present.

7.3 Administration Procedure

Subcutaneous administration

- Use 15mg/3ml ampoules to minimise the volume administered.
- Inject through a Saf-T-Intima (butterfly).
- The Saf-T-Intima should be flushed with 0.2ml of water for injection after administration of medication.
- Can be administered via a continuous subcutaneous infusion pump (Niki T34).

Intranasal administration

- Ensure patient is seated upright with head upright. Avoid tilting head back if possible as this can cause solution to be swallowed.
- Hold the bottle upright and instil one spray into one or both nostrils. There is no need to breathe/inhale the dose in.
- Dose can be given up to every ONE hourly as required with the response closely monitored.
- Dose may be up-titrated according to response.
- Can be administered via the buccal route (squirt dose between the lower gum and the cheek) if indicated.

8. Observation and Monitoring

Observe patient for excessive sedation.

9. Potential Adverse Effects

- Excessive sedation
- Hypotonia
- Ataxia
- Confusion
- Dizziness
- Respiratory depression
- Amnesia
- Fatigue
- Skin rash
- Pruritis
- Hypotension
- Hallucinations
- Paradoxical reactions (especially in elderly) e.g. agitation, delirium, insomnia, excitement, involuntary movements, rage[1, 6]

Midazolam Subcutaneous and Nasal - Palliative Care (Adults)

10. Drug Interactions

10.1 Medications which increase midazolam plasma concentrations

- CYP3A4 inhibitors can inhibit hepatic metabolism of midazolam resulting in a prolonged and more pronounced effect. (e.g. cimetidine, erythromycin, clarithromycin, diltiazem, verapamil, HIV protease inhibitors, haloperidol, ketoconazole, fluconazole, voriconazole and itraconazole)1, 3, 5, 6
- Sodium valproate can displace midazolam from its binding sites and may increase the response to midazolam.[1]

10.2 Medications which reduce midazolam plasma concentrations

CYP3A4 inducers (e.g. carbamazepine, high dose dexamethasone, phenobarbital, phenytoin and rifampicin)[2, 3, 5, 6]

10.3 Other

Increased effect of midazolam with CNS depressants (e.g. benzodiazepines, opioids, tricyclic antidepressants)[1, 3]

11. References

1	Medsafe Website – Midazolam Datasheet https://www.medsafe.govt.nz/profs/datasheet/m/mylanmidazolaminj.pdf [cited 02/12/2019]
2	Twycross R, Wilcock A, Howard P (eds). Palliative Care Formulary 6th edition. United Kingdom: Pharmaceutical Press - Palliativedrugs.com Ltd; 2017.
3	Macleod R, Macfarlane S. The Palliative Care Handbook. 9th ed. HammondCare: Hospice NZ; 2019
4	Back I et al (eds). Palliative Medicine Handbook Online edition. BPM Books, Cardiff, UK. http://book.pallcare.info [cited 02/12/2019]
5	Dickman A, Schneider J. The Syringe Driver – Continuous subcutaneous infusions in palliative care. 3rd ed. New York: Oxford university press; 2011.
6	New Zealand Formulary online, release v89-1 Nov 2019 – Midazolam monograph. http://nzf.org.nz [cited 02/12/2019]