Morphine - Palliative Care (Adults)

Contents

1. Overview

Purpose

This protocol outlines the administration, prescribing and monitoring of morphine at Te Whatu Oar - Waitematā.

Scope

All medical and nursing staff

⚠ This guideline is for use in the context of Palliative Care ONLY.

Note: Morphine is the 'gold standard' strong opioid analgesic and should be used first line where possible.

When prescribing morphine always consider prescribing laxatives and antiemetics.

Morphine - Palliative Care (Adults)

2. Presentation

Formulation	Brand Name	Strength
Morphine Sulfate Ampoules	DBL®	10mg/ml, 30mg/ml
Morphine Tartrate Ampoules	DBL®	120mg/1.5ml
Morphine Oral Immediate Release	Sevredol®	10mg, 20mg
Morphine Oral Immediate Release Liquid	RA-Morph®	1mg/ml*
Morphine Oral Sustained Release Capsules	m-Eslon SR®	10mg, 30mg, 60mg, 100mg
Morphine Oral Sustained Release Tablets	Arrow-Morphine LA®	10mg, 30mg, 60mg, 100mg

***Note:** Other concentrations of morphine liquid (2, 5, and 10 mg per ml) are available but are not used in Te Whatu Ora – Waitematā for safety reasons. Always establish and prescribe the patient's current dose in mg (NOT in ml), as there is potential for confusion if the patient is using a higher concentration in the community. (For example 1 ml of the lowest concentration is 1mg, whilst 1 ml of the highest concentration is 10 mg)

3. Indications

Licensed:

- For moderate to severe pain that responds to opioids.

Unlicensed:

- Cough
- Diarrhoea
- Severe shortness of breath.[2]

4. Contraindications and Precautions

Contraindications:

- Patients with hypersensitivity to morphine
- Severe renal impairment
- Acute severe airways disease
- Severe liver disease or incipient hepatic encephalopathy
- Gastrointestinal obstruction
- Patients on monoamine oxidase inhibitors (MAOIs) or within the previous 14 days.[1]

Precautions:

- Hepatic impairment
- Respiratory depression
- Renal impairment
- Convulsive disorders
- Brain tumour/head injuries
- Severe CNS depression
- Patients with raised intracranial pressure
- Arrhythmias
- Elderly patients.[1]

Morphine - Palliative Care (Adults)

5. Mechanism of Action

Morphine is derived from opium and acts as an opioid agonist, binding to receptors in the brain, spinal cord and other tissues. Morphine binds to these *mu* receptors that are widely distributed throughout the central nervous system, being present in the highest concentration in the limbic system.

Morphine primarily acts on the central nervous system and organs containing smooth muscle.[1]

Morphine is metabolised in the liver to morphine-3-glucuronide (M3G), the main metabolite, and morphine-6-glucuronide (M6G). It is thought that M6G is active and more potent than morphine. M3G is inactive but accumulation of this has been thought to be the cause of morphine hyperalgesia. The metabolites are excreted renally.[9]

5.1 Onset and Duration of Action of Morphine

Route	Onset	Tmax (range)	Peak effect	Duration (approx)
Oral – Immediate Release	15-40 min	1 hour (15min – 3.5 hours)	≤60 min	4 hours
Oral – Sustained Release	40 min – 1 hour	3.6 hours (1.6 – 5.5 hours)	N/A	12 hours
Subcut bolus	15 - 20 min	15min (10 – 15min)	50-90 min	4 hours
IV bolus	2 - 5 min	<5 min	20 min	4 hours

6. Dose

6.1 Introduction

Morphine is classed as a strong opioid at level 3 of the World Health Organisation (WHO) pain relief ladder[3]. It is appropriate for patients with moderate to severe pain that is opioid responsive.

Before prescribing morphine, conduct a pain assessment and determine the likely cause of pain so the most effective management can be implemented. Refer to the *Te Whatu Ora – Waitematā Pain Management – Palliative Care guideline*.
If the pain is mild to moderate, consider starting with regular non-opioid analgesia (e.g. paracetamol, non-steroidal anti-inflammatory). If the pain is not adequately controlled with these analgesics, or patient has moderate to severe pain, use morphine as first line analgesia (or other opioids such as oxycodone or fentanyl if there is renal impairment or contraindication to morphine). In those with a history of "allergy" or intolerance to morphine, determine the context in which this occurred in the past before precluding the use of morphine. Refer to *Te Whatu Ora – Waitematā Pain Management – Palliative Care*.

Each patient has a unique sensitivity/response to morphine so start with small doses and titrate according to response.

Despite careful titration of morphine, some individuals will have intolerable side effects or poor analgesic response. If this happens, the following steps should be taken:

1. Review pain diagnosis
    - Some pain respond poorly to opioids e.g. neuropathic pain
    - Incident pain may be better treated with another approach – *seek advice from the Palliative Care team/Acute Pain service*

Morphine - Palliative Care (Adults)

- Colicky abdominal pain due to bowel obstruction may be better treated with an antispasmodic e.g. hyoscine butylbromide.

2. Ensure adequate management of side effects
   - REGULAR antiemetics via PARENTERAL/SUBCUTANEOUS route if nausea/vomiting is a problem
   - REGULAR laxatives if constipation is a problem.

In some cases it may be worth 'switching' morphine to another opioid as there may be individual variability in response to opioids. A systematic review showed no difference in side effect profile between morphine and oxycodone.[4] Fentanyl is likely to be less constipating and may cause less nausea than morphine – however it is not available in the oral route.

⚠ Use a lower dose of morphine in frail/elderly patients, opioid naïve patients and in those with severe hepatic impairment or mild to moderate renal impairment (CrCl 30-50ml/min). Morphine should generally be avoided in severe renal impairment (CrCl <30ml/min) – consider using other opioids (e.g. oxycodone – see *Oxycodone – Palliative Care (Adults)* or fentanyl – see *Fentanyl Subcutaneous and Nasal – Palliative Care (Adults)*)

6.2 Oral Morphine

Starting Dose if *Opioid Naive*

Generally patients should be prescribed short acting morphine initially and converted to sustained release morphine after 1-2 days according to patient's opioid requirement.[2,5]

Immediate release morphine (RA Morph®/Sevredol®)

Recommended starting dose:

- **2.5 – 5mg PO q 1 hourly PRN**[5,8]

If three or more PRN doses are required in a 24 hour period, consider increasing the PRN dose and/or starting sustained release morphine. Also consider re-review of the pain diagnosis.

Converting to Sustained Release Morphine

To change to a sustained release oral morphine preparation (e.g. m-Eslon SR®):

- Calculate the total amount of morphine the patient has required over the past 24 hours and then divide by 2 to get the equivalent dose of sustained release morphine[2]

E.g. **20mg** oral immediate release morphine over 24 hours = **10 mg BD** sustained release oral morphine

- m-Eslon SR® should be charted as a BD dose (q12 hourly)
  - a three times daily (q8 hourly) dosing schedule may be required in patients who experience consistent breakthrough pain towards the end of the 12 hour period - *seek advice from the Palliative Care team/Acute Pain service*
- Chart PRN doses when charting sustained release morphine
  - PRN doses should be around **1/6th** of the total daily dose and charted q 1 hourly[2]

Morphine - Palliative Care (Adults)

Increasing Doses of Sustained Release Morphine

- Consider increasing the dose of sustained release morphine (e.g. m-Eslon SR®) if more than three PRN doses has been used in 24 hours[2]
- Generally the dose should not be increased more frequently than every 48 hours
- When the sustained release morphine dose is increased, the PRN dose should also be increased so it remains 1/6th of the total daily dose

Consider seeking advice from the Palliative Care or Acute Pain team if:

- Pain is increasing and the patient is using more than three PRN doses for breakthrough pain per 24 hours OR
- The patient is on high doses of morphine e.g. total oral morphine dose > 400mg per 24 hours[6]

6.3 Subcutaneous Morphine

Starting Doses if *Opioid Naive*

Subcutaneous bolus dosing

Start with PRN subcutaneous morphine initially - recommended starting dose:

- **2.5mg subcut q 30min PRN**

Continuous subcutaneous infusion (CSCI)

If PRN subcutaneous medication does not provide sustained symptom relief or more than 3 doses are required in a 24 hour period, consider the use of a CSCI of morphine via a Niki T34 pump:

- Calculate the total amount of PRN morphine the patient has required over the last 24 hours and prescribe this amount as a 24 hour continuous infusion[2]
- Also chart about 1/6th of the total dose as a PRN dose q 30min for breakthrough pain
- Review doses of background and PRN morphine daily.

If the patient has not had a 24 hour trial of subcut PRN morphine, a total 24 hour dose requirement can often be extrapolated from adding up morphine requirement over the preceding 6 – 18 hours.

If a patient has had no subcut morphine to guide dose selection, start with a dose of 10mg over 24 hours and review after 24 hours, increasing or decreasing dose as necessary according to PRN usage.[2] A dose of 5mg over 24 hours could be considered for the elderly or those with severe hepatic impairment or mild to moderate renal impairment.

6.4 Other Routes

Intravenous (IV)

Use the *Te Whatu Ora – Waitematā Opioid protocol – Oral and IV – Acute Pain (Adults)*[7] for palliative patients who are opioid naïve.

- Permitted dosing via the protocol (0.5 – 2 mg morphine per dose) may be inadequate for palliative patients who are on long-term opioids as they generally require larger doses than provided for in the protocol. However larger IV bolus doses are not recommended due to side effects caused by rapid achievement of peak plasma levels.

Morphine - Palliative Care (Adults)

- Large bolus doses of morphine can be safely administered by the subcutaneous route as peak plasma levels are lower with subcut administration and reached over a longer time frame compared to IV administration.

Topical, nebulised and rectal (suppositories) morphine:

- These routes are occasionally used but are out of the scope of this document
- There is no evidence to support the use of nebulised morphine.[2]

6.5 Suggested Conversion Ratios

The systemic bioavailability of oral morphine varies widely between individuals so equianalgesic dose conversion tables have limitations. They do however provide a safe guide when converting opioids from oral to parenteral route or one opioid to another. If in doubt, talk with a member of the Palliative Care Team.

Route 1	Route 2	Ratio	Example
PO morphine	SC morphine	2:1 or 3:1*	30mg PO morphine = 10 - 15mg SC morphine
PO morphine	PO oxycodone	2:1**	10mg PO morphine = 5mg PO oxycodone
PO oxycodone	PO morphine	1:1.5**	5mg PO oxycodone = 7.5mg PO morphine
PO morphine	SC oxycodone	2:1	10mg PO morphine = 5mg SC oxycodone
SC morphine	SC oxycodone	1:1	5mg SC morphine = 5mg SC oxycodone
IV morphine	SC morphine	1:1[#]	1mg IV morphine = 1mg SC morphine
SC morphine	SC fentanyl	100:1	1mg (1000mcg) SC morphine = 10mcg SC fentanyl

Note: PO = oral, SC = subcutaneous, IV = intravenous

* The equianalgesic ratio is somewhere between 2:1 and 3:1. Dividing the oral dose by 2 may result in a slight increase in analgesic effect; dividing by 3 may result in a slight reduction in analgesia which may be appropriate in some cases e.g. if concerned about oral absorption or patient adherence.

**When converting from oral morphine to oral oxycodone a ratio of 2:1 should be used. When converting from oral oxycodone to oral morphine a ratio of 1:1.5 should be used. Each conversion is conservative. The safety margin results in a slightly lower dose of the new opioid to take account of wide inter-individual variability in response to opioids.

[#]Recommend a 1:1 ratio although some centres suggest 1mg IV morphine = 2mg subcut morphine, which is conservative when converting from subcut to IV but may be excessive when converting from IV to subcut.[2]

Converting from oral to subcutaneous morphine

- If a patient has been taking oral morphine but becomes unable to take oral medication for any reason, the dose of oral morphine should be converted to a subcutaneous dose.
- Note there is considerable inter-individual variability in the equianalgesic conversion ratio of morphine oral to subcut.
- **When converting the patient's usual 24 hour oral dose to a continuous subcut infusion** the safest approach is to convert only the patient's current background dose (don't include PRN doses) by dividing by 2 or 3 and then up titrate the next day according to the PRN usage in last 24 hours.

Morphine - Palliative Care (Adults)

7. Administration

7.1 Oral

- **m-Eslon SR® capsules**
  - Can be opened and sprinkled on soft food as long as the beads are not crushed or chewed.
  - Can be administered via a feeding tube provided the gauge is 16 French (internal diameter 2.5 mm) or larger.[1] Open capsule, put granules down the tube then flush with 30 – 50 ml water.[10] Please discuss with pharmacy if you wish to use this method of administration.
- **Arrow-Morphine LA® tablets must NOT be crushed.**
- **Sevredol®** tablets can be crushed or cut in half but the liquid is a better choice if the patient has difficulty swallowing.

7.2 Subcutaneous

- Should be injected through a Saf-T-Intima (butterfly).
- The Saf-T-Intima should be flushed with 0.2ml of water for injection after administration of medication.
- The 10mg/ml concentration should be used for subcutaneous PRN boluses.
- Can be administered via a continuous subcutaneous infusion pump (Niki T34).

Diluent

- For subcutaneous bolus administration morphine does not need to be diluted.[8]
- When added to a syringe driver the recommended diluent is water for injection.[2, 8]

Additional Equipment

- Subcutaneous Saf-T-Intima single lumen [ADM140] (*See Te Whatu Ora – Waitematā policy Palliative Care - Subcutaneous Site Selection, Insertion and Monitoring of BD Saf –T- Intima Cannula*).
- Continuous subcutaneous infusion pump (Niki T34) if required.

Compatibility

Morphine sulphate is compatible with:

water for injection, 0.9% sodium chloride, metoclopramide, cyclizine, levomepromazine, hyoscine hydrobromide, hyoscine butylbromide, dexamethasone, ketamine, octreotide, midazolam, haloperidol, clonazepam, ondansetron.[2, 6, 9]

Morphine tartrate is compatible with:

water for injection, 0.9% sodium chloride, dexamethasone, metoclopramide, clonazepam, ketamine, cyclizine, levomepromazine, midazolam, hyoscine hydrobromide.[2, 6, 9]

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

8. Observation and Monitoring

- Observe patient for respiratory depression
- Monitor blood pressure and for orthostatic hypotension
- Monitor for excessive drowsiness
- Monitor for nausea and vomiting, especially at initiation of morphine
- Monitor for constipation and urinary retention.[1, 8]

Morphine - Palliative Care (Adults)

9. Adverse Effects

- Constipation
- Sedation
- Respiratory depression/apnoea
- Dizziness
- Confusion, delirium, hallucinations
- Nausea and vomiting
- Sweating
- Dysphoria and euphoria
- Myoclonic jerks
- Hypotension
- Dry mouth
- Urticaria
- Itch (pruritis)
- Urinary retention
- Blurred vision
- Diplopia/miosis
- Local irritation at injection site
- Palpitations
- Dependence/tolerance[1, 2]

10. Drug Interactions

- Monoamine oxidase inhibitors (MAOIs)
    - Non-selective MAOIs intensify the effects of morphine and other opioids which can cause anxiety, confusion and significant respiratory depression sometimes leading to coma
    - Avoid concomitant use and for 2 weeks after stopping MAOIs.
- Additive effects with central nervous system depressants e.g. benzodiazepines, tricyclic antidepressants, other opioids and alcohol.[1]
- Medications that affect hepatic or renal function may impair morphine clearance.[9]

11. References

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