Levomepromazine (Methotrimeprazine) Palliative Care (Adults)

Contents

1. Overview

Purpose

This protocol outlines the administration, prescribing and monitoring of levomepromazine (methotrimeprazine) at Te Whatu Ora - Waitematā.

Scope

All medical and nursing staff.

⚠ This guideline is ONLY for use in patients with advanced life limiting illness receiving a palliative care approach to care.

2. Presentation

- Levomepromazine (methotrimeprazine) 25mg/mL injection.
- Levomepromazine (methotrimeprazine) 25mg and 100mg tablets (Swiss Sanofi Nozinan® brand).
- Levomepromazine (methotrimeprazine) maleate 25mg and 100mg tablets (NZ Sanofi Nozinan® brand).

The NZ Sanofi levomepromazine (Nozinan®) 25mg tablets have been replaced with the Swiss Sanofi Nozinan® formulation temporarily due to manufacturing issues. The NZ Nozinan® 100mg tablets will be supplied until stock runs out and then these will also be replaced with the Swiss Sanofi formulation.
Please note that NZ Sanofi levomepromazine and Swiss Sanofi levomepromazine are NOT bioequivalent.

⚠ The Swiss Sanofi tablets have “levomepromazinum” on it and will be over-labelled in English. Swiss Sanofi tablets are beige coloured; whereas NZ Sanofi tablets are white.

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3. Indication

Licensed[1, 2]:

- Terminal pain with accompanying restlessness, anxiety or distress
- Acute psychotic symptoms
- Schizophrenia.

Note: In New Zealand the subcutaneous route is licensed to 200mg/24hours, and the oral route is licensed to a usual dose of 100-200mg.[1]

Unlicensed[2, 3]:

- Nausea and vomiting
- Delirium.

4. Contraindications and Precautions

Contraindications[1]

- Hypersensitivity to levomepromazine (methotrimeprazine).

Precautions[1, 2]

- Parkinsonism
- Postural hypotension
- Epilepsy
- Hypothyroidism
- Myasthenia Gravis
- Liver dysfunction
- Renal and hepatic impairment
- Cardiac disease
- Stroke
- Dementia.[1,2]

5. Mechanism of Action

Levomepromazine (methotrimeprazine) is a neuroleptic agent. It has analgesic, anti-emetic, anti-histamine, anti-adrenergic and potent sedative effects by blocking the dopamine, serotonin, histamine, adrenergic and acetylcholine receptors. Its precise mechanism of action is unknown. Levomepromazine is metabolized by the liver to 2 major active metabolites and is excreted via the kidneys. It accumulates in the brain tissue, where its elimination half life is one week. The oral bioavailability of levomepromazine is 20 to 50%.[1, 2, 6]

6. Dose

The conversion ratio for oral (PO) to subcutaneous (subcut) doses varies in clinical use from centre to centre. Because small doses (25mg or less) are generally used, we recommend the use of a conversion ratio of **1:1.**[2] *For higher doses, seek advice from the Palliative Care team.*

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A low dose should be started and titrated upwards depending on individual response as it can cause excessive sedation even at small doses.

Start with lower doses in elderly patients and those with renal or hepatic impairment (*see table below).*

In this protocol, doses of oral tablets are expressed as *levomepromazine maleate* - the NZ Sanofi levomepromazine (Nozinan®) formulation.

The current NZ Sanofi levomepromazine (Nozinan®) 25mg tablets has been temporarily replaced with Swiss Sanofi Nozinan® formulation. The NZ Sanofi levomepromazine (Nozinan®) 100mg tablets remain available until stock runs out.

1 x NZ tablet ≈ 0.75 x Swiss tablet

Patients already taking the NZ levomepromazine tablets require a review of their prescription and be monitored for altered clinical effect or toxicity. Patients taking levomepromazine dose of 25mg or less do not need to have their dose automatically reduced as a result of this stock change – *seek advice from the Palliative Care team*.

Indication	STAT and initial PRN dose	Maintenance Dose	
		Oral dose range over 24 hours (in divided doses)	Subcut dose range over 24 hours (in divided doses or CSCI[a])
Antiemetic[2]	6.25mg PO/subcut nocte[b] AND 6.25mg PO/subcut q4 to 6 hourly PRN (maximum 25 mg in 24 hours)[c]	6.25 – 25mg Consider switching to subcut route if no symptom response	6.25 – 25mg[b]
Terminal agitation[2]	6.25mg PO/subcut STAT and 6.25mg PO/subcut q1 hourly PRN[c]	Use subcut route	12.5 – 100mg

[a] CSCI = continuous subcutaneous infusion

[b] In elderly/frail patients and those with renal/hepatic impairment, consider starting a lower dose at 3.125mg

[c] Levomepromazine can cause sedation even at low doses – best practice is to administer STAT/regular dose at night if possible.

7. Administration

7.1 Diluent

- For subcutaneous bolus administration levomepromazine does not need to be diluted.
- When added to a syringe driver the recommended diluent is **sodium chloride 0.9%.**[2]

7.2 Additional Equipment

- Subcutaneous Saf-T-Intima single lumen [ADM140] (*refer to 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.

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7.3 Compatibility

Compatible with:

- Sodium chloride 0.9% (preferred diluent), water for injection.
- Morphine sulfate, morphine tartrate, methadone, metoclopramide, hyoscine hydrobromide, hyoscine N-butylbromide, haloperidol, ketamine, ondansetron, glycopyrrolate, midazolam, clonazepam, fentanyl, oxycodone, cyclizine.[2, 3]

Concentration dependent incompatibility with:

Dexamethasone, octreotide, ranitidine.[2, 3]

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

7.4 Administration Procedure

Subcutaneous administration

- Inject through a Saf-T-Intima (butterfly).
- The Saf-T-Intima should be flushed with 0.2ml of **sodium chloride 0.9%** after administration of medication.
- Can be administered via a continuous subcutaneous infusion pump (Niki T34).

8. Observation and Monitoring

- The injectable preparation contains sulfites and may cause hypersensitivity or anaphylaxis – more common in asthmatic patients.[4]
- Monitor for excessive drowsiness.[1-3]
- Monitor for postural hypotension.[1, 2]
- Monitor for extrapyramidal side effects, particularly in elderly patients and those with Parkinson's.[2, 3]
- Monitor blood sugar levels every SIX hours for 48 hours for those with diabetes or impaired glucose tolerance if appropriate.[1]
- Monitor for irritation at the injection site.[4]

9. Possible Adverse Effects

- Hypotension (common in elderly/ambulatory patients)
- Drowsiness
- Disorientation / confusion
- Somnolence
- Dry mouth
- Extra-pyramidal side effects (more common with high dose)
- Photosensitivity
- Allergic skin reactions
- QT interval prolongation (rare)
- Ventricular arrhythmias
- Torsades de pointes.[1-3]

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10. Drug Interactions

- CNS depressants - levomepromazine will enhance the activity of any sedatives or hypnotics (e.g. benzodiazepines, opioids, chlorpromazine, tricyclic antidepressants).[1, 6]
- Increased risk of QT prolongation with other QT prolonging medications (e.g. ondansetron, domperidone, tricyclic antidepressants, theophylline, erythromycin).[2, 6]
- Levomepromazine inhibits CYP2D6 enzyme – monitor for increased effects of drugs metabolised by CYP2D6 (e.g. amitriptyline, fluoxetine, oxycodone, promethazine) or decreased effects (e.g. codeine – due to decreased conversion to morphine).[6]

11. References

1	Medsafe Website – Nozinan Datasheet. https://www.medsafe.govt.nz/profs/datasheet/n/Nozinantabinj.pdf [cited 26/05/2020]
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	Sutherland J et al. (eds). Notes on Injectable Drugs- Adults 7th Edition 2015. New Zealand Hospital Pharmacists' Association, Wellington NZ.
5	Back I et al (eds). Palliative Medicine Handbook Online edition. BPM Books, Cardiff, UK. http://book.pallcare.info [cited 26/05/2020]
6	Dickman A, Schneider J. The Syringe Driver – Continuous subcutaneous infusions in palliative care. 3rd ed. New York: Oxford university press; 2011.