



Leicestershire & Rutland



Palliative Care Prescribing – Drugs for Specialist Recommendation Only

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Description of amendments

New monographs on Levetiracetam (control of epilepsy where someone cannot swallow the oral preparation and alternative measures have been unsuccessful) and Quetiapine (delirium in Parkinson's Disease and related conditions).

Updates on existing medication including revised guidance on Methadone and Naloxone.

Ranitidine GI protection dose for NSAID updated in line with BNF

Version 4

Date: January 2018

Review January 2020

Please note prices are subject to change.

Endorsed by Leicestershire Medicines Strategy Group

PALLIATIVE CARE GUIDELINES

Shared care has been defined as the mechanism of sharing patient care between primary and secondary care providers.

Within a palliative care setting input into patient care may be from many health professionals. During ongoing care medical support and information may be sought from palliative care clinicians.

Palliative Care Clinician Responsibilities

- Liaison with general practitioner (GP) to share patient care and ongoing problems
- Responding to issues raised by the GP caring for the patient
- Advising GP on therapies which may be of benefit for individual palliative care problems. Many of these drugs may not be licensed for the specific situation although the product will have a licence for other indications outside a palliative care setting.
- Reviewing patient at appropriate clinic if referred.

GP Responsibilities

- Monitor the patients overall well-being and raise any concerns with the palliative care consultant
- Prescribing medication listed below following discussion or liaison with palliative care
- Ensuring advice is sought from palliative care on any issue causing concern.
- Altering dosage or therapy following palliative care advice and the guidelines below

Drugs covered by the guidelines – **WE RECOMMEND THESE SHOULD ONLY BE STARTED BY OR IN LIAISON WITH A PALLIATIVE CARE DOCTOR.**

- [Atropine Eye Drops \(used orally\)](#)
- [Fentanyl sublingual tablets](#)
- [Furosemide subcutaneous infusion/bolus](#)
- [Ketamine](#)
- [Ketorolac](#)
- [Levetiracetam](#)
- [Methadone](#)
- [Methylnaltrexone](#)
- [Midazolam](#)
- [Octreotide](#)
- [Olanzapine](#)
- [Ondansetron/Granisetron](#)
- [Quetiapine](#)

For information regarding **Alfentanil** see [ICP Drug Prescribing in Advanced Kidney Disease \(Appendix 1\)](#)

It is also recognised that other drugs commonly used in palliative care syringe drivers are not licensed once mixed in a syringe driver. Guidance on such combinations can be found in [Guide to Prescribing in Advanced Malignancy](#)

All costs correct January 2018.

Contact Support and Advice

[Guide to Prescribing in Advanced Malignancy](#) Dr Nicky Rudd, Dr Caroline Cooke.

Palliative Care Formulary version 5.

LOROS advice line 0116 2318415

UHL Specialist Palliative Care Teams on Ex 5414 (LRI); Ex 3540 (GH); Ex 4680 (LGH)

Palliative Adult network Guidelines - <http://book.pallcare.info/>

GUIDELINES FOR THE USE OF ATROPINE EYE DROPS ORALLY

Indications

Drooling, due to reduced swallowing e.g. in motor neurone disease, may be improved with antimuscarinic medication, including Atropine Eye Drops 1% taken orally.

Atropine (as eye drops) are often used alone but may be used in combination with other antimuscarinics (given orally, subcutaneously or by enteral or transdermal routes) to achieve the required balance of saliva production.

Pharmacology

Atropine is a tertiary amine that exerts its effect on saliva production via its antimuscarinic action (both locally and via oesophageal vagal fibres). The dose required to reduce saliva is typically less than that which affects other muscarinic receptors.

Pharmacokinetics

Atropine is readily absorbed orally and sublingually and has a plasma half-life of 4 hours.

Dosage and administration

One to four drops of Atropine Eye Drops 1% is used up to 4 times day and titrated to effect.

Cautions

Use with caution in myasthenia gravis, glaucoma, where tachycardia may be an issue (heart failure, angina) and bladder outflow obstruction.

Monitoring

No specific monitoring is indicated.

Drug Interactions

Antimuscarinic drugs may impair the effect of prokinetic drugs e.g. domperidone, metoclopramide.

Side Effects

Dry mouth, blurred vision, tachycardia, constipation, retention of urine, reduced sweating.

Cost

Jan 2018 Drug Tariff price – Atropine 1% eye drops 10ml - £132.25

An alternative option maybe Minims Atropine eye drops 1% 0.5ml UDV – 20 unit dose DM+D Price Jan 2018 £15.10

GUIDELINES FOR THE USE OF SUBLINGUAL FENTANYL

Fentanyl is rapidly absorbed through the tissues of the mouth (cheeks, under tongue, palate). This allows rapid onset of action. Any fentanyl that is swallowed has much less effect.

Indications

Analgesia and:

- For patients with swallowing difficulty
- For patients who need rapid onset analgesia (e.g. for incident pain or dressings)
- For patients who need short lived breakthrough analgesia (e.g. for incident pain or dressings)
- For patients with poor gastrointestinal absorption
- For patients who are intolerant of other opioids

Dosage and administration ¹

- There are 4 licensed products: Abstral (sub-lingual tablet); Effentora (buccal/sublingual tablet); PecFent and Instanyl (intra-nasal sprays).
- In Leicestershire, only **Abstral** has been evaluated and approved for use by the UHL Therapeutics Advisory Service and LMSG and only **then after discussion with a palliative care specialist**.
- Onset of action is from 10-15 minutes
- Time to peak plasma concentration about 20-40 minutes
- Duration of action about 1-3 hours – should not be used more frequently than 2 hourly as may accumulate and a maximum of four doses in 24 hours.

How to use:

See product information for titration **and discuss with a palliative care specialist**.

Cautions in Use

For full list, see Abstral SPC

Drowsiness, dizziness, nausea.

Contraindications

As per opioids.

Monitoring

Assess analgesic response and any side effects to initial dose and titrate to effect **as discuss with a palliative care specialist**.

Drug Interactions

As per opioids.

Side Effects

As per opioids.

Cost

Abstral £50 per 10 tablet pack for all strengths. Following dose titration ensure correct strength is prescribed.

References

1. Fentanyl - Palliative Care Formulary 6th Edition
2. <http://www.medicines.org.uk/emc/medicine/21371>

GUIDELINES FOR THE USE OF SUBCUTANEOUS FUROSEMIDE

Indications

Patients with heart failure are often prescribed diuretics as part of their drug treatment. If they become more symptomatic (e.g. increasing oedema, weight and/or breathlessness) while taking oral diuretics, treatment with parenteral (normally intravenous) furosemide may be helpful. In the past this has usually necessitated admission to an acute hospital. Giving furosemide via the subcutaneous (s/c) route may be an alternative way of managing these patients, especially when admission to hospital may be deemed inappropriate, for instance at the end of life. It may also allow discharge from hospital for those patients require ongoing treatment with parenteral diuretics.

Furosemide is effective when given subcutaneously to healthy volunteers and has similar local complication rates as subcutaneous saline ¹. In one survey, it was used by up to 69% of centres caring for an elderly population, but its effectiveness was not examined ². In theory, the dose used subcutaneously should be the same as the dose used intravenously, unless there is a reaction at the site of administration that prevents absorption. It was as well tolerated locally when given subcutaneously as normal saline ¹. Some practitioners have given it 20mg (2ml) s/c prn, whilst others have infused it ³. The subcutaneous route is unlicensed but should be seen as a legitimate aspect of clinical practice ⁴.

Dosage and administration

Consult with cardiology, medical or palliative medicine consultant or SpR to discuss suitability of initiation of treatment. Liaise with GP and district nursing services.

Start with the same dose s/c as the patient was previously taking orally, or you would be using if the patient was going to have intravenous Furosemide. If the patient was taking bumetanide the ratio is oral Furosemide 40mg = Bumetanide 1mg

In patients who are dying and who are drinking less, reducing the dose of diuretic in line with fluid status may be appropriate.

Continuous Subcutaneous Infusion

Administer the dose by continuous subcutaneous infusion via a **McKinley T34** (24 hour) syringe driver diluted with Sodium chloride 0.9%. It may be infused over 24 hours. If a large dose is required, two syringe drivers may be used concurrently. There is limited data on drug compatibility so it is **not** recommended to mix furosemide with other drugs at present.

Avoid using oedematous areas as infusion sites due to possible reduced absorption, and monitor the site as you would for any other subcutaneous infusion.

Bolus dosing

Some practitioners have given it 20mg (2ml) s/c prn.

Cautions in Use

Use with caution in hypotension, impaired micturition, gout, diabetes or prostatic enlargement.

Avoid using oedematous areas as infusion sites due to possible reduced absorption.

Relative Contraindications

Hypovolaemia, dehydration, severe hyponatraemia or hypokalaemia. Comatose or precomatose states associated with liver cirrhosis. Renal failure due to nephrotoxic or hepatotoxic drugs. Anuria.

Monitoring

Monitor clinical symptoms and signs (breathlessness, weight, oedema) as normal. Measuring serum urea and electrolytes if appropriate (e.g. if worsening renal function would not change your management, consider not measuring). Adjust the dosage accordingly. Hospital at home may be an appropriate service if close monitoring is needed.

Monitor the site as you would for any other subcutaneous infusion for signs of irritation or infection.

For further advice, please contact your local clinical nurse specialist in heart failure or LOROS (0116 2318415).

Drug Interaction

Diuretic effect may be antagonised by concomitant use of corticosteroids. Diuretic effect may be antagonised by Ketorolac. Increase risk of nephrotoxicity with NSAIDs.

Side Effects

Mild gastrointestinal disturbances, hyperglycaemia, electrolyte disturbances, tinnitus and deafness. Hypersensitivity reactions including rashes and anaphylaxis.

Cost

10mg/ml amp. 5ml= 45p 25ml=£2.50

References

1. Verma AK, da Silva JH, Kuhl DR. Diuretic effects of subcutaneous furosemide in human volunteers: a randomized pilot study. *The Annals of Pharmacotherapy* 2004 April; **38**: 544-549
2. Fonzo-Christe C, Vukasovic C, Wasilewski-Rasca A-F, Bonnabry P. Subcutaneous administration of drugs in the elderly: survey of practice and systemic literature review. *Palliative Medicine* 2005; **19**: 208-219
3. Palliativedrugs.com website bulletin board, search term "furosemide"
<http://www.palliativedrugs.com/pdi.html> accessed 21/04/06
4. The use of drugs beyond licence in palliative care and pain management. A position statement prepared on behalf of the Association for Palliative Medicine and The Pain Society.
http://www.palliative-medicine.org/resources/images/Drugs_doc.pdf
accessed 26/05/06
5. Palliative Care Formulary 6th Edition

GUIDELINES FOR THE USE OF KETAMINE

This would normally be started in a secondary care setting by a palliative care specialist.

Indications

Ketamine is an anaesthetic agent, but in the palliative care setting it can be used for neuropathic, ischaemic, inflammatory or myofascial pain that is not responding to strong opioid analgesia.¹ It should be noted that ketamine is unlicensed for pain control.

Ketamine is a potent NMDA receptor channel blocker. The NMDA glutamate receptor is a calcium channel in the dorsal horn of the spinal cord that is involved in central sensitisation.^{1,2}

Dosage and administration

Orally

- Start at 10 to 25mg tds-qds and prn (max hourly)
- Increase dose in steps of 10-25mg up to 50mg qds
- Maximum reported dose is 200mg qds

Oral ketamine tastes very bitter, discuss with pharmacy for alternative preparations.

Subcutaneously

- Start at 10 to 25mg prn (<500 micrograms/kg)
- If necessary increase dose in steps of 25-33%

Continuous Subcutaneous Infusion

- Start at 1 to 2.5mg/kg/24hours. Typically 100 to 300mg over 24 hours
- If necessary increase by 50-100mg daily.

With higher doses consider reducing the dose of morphine if the patient becomes drowsy.

If a patient experiences hallucinations the dose of ketamine should be reduced and given diazepam 5mg stat and 5mg at night, or midazolam 5mg sc stat and 5 to 10mg via CSCI or haloperidol 2 to 5mg PO stat and 2 to 5mg at night. **These medications can be prescribed in anticipation.**

Ketamine can irritate the skin and so it should be diluted in the largest volume of sodium chloride 0.9% possible. If it is to be mixed with other drugs in the same syringe driver compatibilities should be checked.

Conversion of oral ketamine to subcutaneous ketamine for pain control

- Initially use a 1:1 conversion.
- Review as individual patients may vary and require further titration.

Prescribing-controlled drug requirements

Ketamine is a controlled drug. The oral solution (50mg/5ml x 500ml) is available via pharmacy from Rosemont Pharmaceuticals LTD (specials). Other available formulations include 50mg/ml injection in a 10ml vial.

Pharmacokinetics

Oral Ketamine undergoes extensive first pass hepatic metabolism to norketamine. It is thought that oral and subcutaneous doses are equipotent. In some studies it has been reported that the maximum blood concentration of norketamine is greater after oral administration than after injection and it is thought that the extensive first pass metabolism is responsible for this. Some times when converting from a parenteral dose to an oral dose after several weeks a smaller oral dose can be used. Ketamine can be used safely in patients with renal impairment.^{1,3}

Cautions in Use

Epilepsy, hypertension, cardiac failure, symptomatic angina, cerebrovascular disease. Urinary tract toxicity – urinary tract symptoms (frequency, urgency, incontinence, dysuria and haematuria) can be caused by ketamine. The underlying pathophysiology is not clear and usually patients are on significant doses for many months before developing toxicity. If symptoms do occur with no evidence of bacterial infection then the ketamine should be stopped.^{1,2}

Contraindications

Any situation in which an increase in blood pressure or intracranial pressure would be hazardous, acute intermittent porphyria^{1, 2} and hypersensitivity

Monitoring

Ensure skin site does not show signs of irritation. If irritated check dilution and compatibility.

Drug Interaction

Plasma concentration is increased by diazepam.¹

Side Effects

The most common side effects are tachycardia, intracranial hypertension, confusion, delirium, vivid dreams, hallucinations and feelings of detachment from the body.^{1,4}

Cost

500mg in 10ml injection £4.32

50mg in 5ml oral solution x 500ml £168

References

1. Ketamine. www.palliativedrugs.com
2. Twycross R and Wilcock A. Editors-in-Chief. Palliative Care Formulary (PCF5). Palliativedrugs.com 5th Edition Nottingham 2014.
3. Stannard C, Booth S. Pain. Churchill Livingstone 2nd Ed London 2004.
4. Binns A. Ketamine in Palliative Care. www.medicineau.net.au.

GUIDELINES FOR THE USE OF KETOROLAC

Indications

Severe cancer pain poorly responsive to the maximum doses of other Non Steroidal Anti-Inflammatory Drugs (NSAIDs) combined with a strong opioid
Ketorolac can offer significant analgesia when other NSAIDs have not, particularly in bony or inflammatory cancer pains. Patients are counselled that it may have more side effects. The usual aim is to use for 2 weeks or less pending other treatments (e.g. radiotherapy) but it has been used for up to six months without undesirable side effects.

Dosage and administration

20 to 30mg tds can be given by subcutaneous injection but is better tolerated by continuous subcutaneous infusion (CSCI).

60mg/24 hours by CSCI (maximum dose in patients over 65 or under 50kg). Can be increased by 15mg/24h up to 90mg/24h maximum.

Co-prescribe a gastro-protective drug H2 antagonist or PPI (e.g. ranitidine 300mg bd or lansoprazole 30mg od).

Cautions in Use

Caution in patients with renal cardiac or hepatic impairment. Ketorolac may impair renal function. The dose should be kept as low as possible and renal function monitored. Use with caution in patients with a history of peptic ulceration.

Contraindications

Contraindicated in patients with hypersensitivity to aspirin or other NSAID, coagulation defects or severe heart failure.

Monitoring

Check for signs of gastrointestinal side effects and skin reactions at site of infection.

Drug Interactions

Furosemide (reduced diuretic response and increased risk of nephrotoxicity), ACE inhibitors (increased risk of renal impairment). Do not give concomitantly with other NSAID

Side Effects

Bleeding and pain at injection sites (others as for NSAIDs – increased risk of GI side effects compared with other NSAIDs).

Cost

30mg/ml £1.1 per amp.

References

1. Twycross R and Wilcock A. Editors-in-Chief. Palliative Care Formulary (PCF5). Palliativedrugs.com 5th Edition Nottingham 2014.

GUIDELINES FOR THE USE OF LEVETIRACETAM INJECTION

Indication

Control of epilepsy where someone cannot swallow the oral preparation and alternative measures have been unsuccessful (eg infusion of midazolam subcutaneously).

Pharmacology

Levetiracetam binds to synaptic vesicle protein SV2A and is presumed to interfere with the release of the neurotransmitter stored within the vesicle.

Levetiracetam is effective for a broad range of seizure types. Its efficacy and tolerability compare favourably to other newer anti-epileptic drugs.³ It is commonly used second-line, or first-line when the seizure type is unclear or when other anti-epileptics are contra-indicated because of co-morbidities.

Bio-availability ≥95% PO.

Onset of action antiepileptic effect generally evident <3 days of starting treatment.

Peak plasma concentration 1–2h.

Plasma half-life 6–8h.

Duration of action 24h.

Dosage and administration

Although unlicensed, a case report and case series (n=15) respectively suggest that administration SC and CSCI are well tolerated.

Usual dose range 500mg to 3g/day.

Use a PO:SC dose ratio of 1:1 and infuse via CSCI using the IV preparation over 24 hours. Water for injection or sodium chloride 0.9% may be used as a diluent. Higher doses (e.g. above 2g/24 hours) may require 2 syringe drivers.

There is currently no information on compatibility with other medications in a syringe driver and therefore should not be mixed with other medications

Cautions

Dose reduction may be required with renal impairment, look for secondary renal impairment in those with hepatic impairment.

Monitoring

Clinical response (e.g. seizure activity)

Drug Interactions

Although caution is advised when **carbamazepine** or **phenytoin** are used in combination with levetiracetam, a clinically significant interaction is unlikely. Consult product literature/BNF

Side Effects

Very common (>10%): fatigue, drowsiness.

Common (<10%, >1%): ataxia, hyperkinesia, tremor, dizziness, headache, diplopia, blurred vision, amnesia, abnormal thinking, attention disturbance, behavioural disturbances (emotional lability, irritability, agitation, hostility/aggression, personality disorders), depression, insomnia, anorexia, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, myalgia, rash, pruritus, thrombocytopenia.

Costs

Levetiracetam 500mg/5ml solution for infusion x 10 vials £127

References

- 1) BNF online accessed July 2017
- 2) <http://www.medicines.org.uk/emc/medicine/32709>
- 3) <http://www.palliativedrugs.com/formulary/en/levetiracetam.html>

GUIDELINES FOR THE USE OF METHADONE and use of NALOXONE

ONLY TO BE INITIATED BY SPECIALIST PALLIATIVE CARE NORMALLY IN A SECONDARY CARE SETTING

Indications

- Poorly controlled pain where intolerable side effects (nausea, vomiting, sedation, hallucinations) have prevented dose escalation of another opioid.
- Refractory pain or difficult pain syndromes (especially neuropathic pain).
- Renal impairment. (Remember to consider other opioids e.g. fentanyl)
- Paradoxical pain with other strong opioids.
- Cough resistant to other opioids

Patients are usually admitted to a specialist palliative care unit when switching from another opioid to methadone. This is to enable a controlled titration period. It is a highly lipophilic drug with a long half life and repeated use leads to an extensive tissue reservoir.

Patients will usually be discharged on a twice daily dose with a prn dose that can be used no more often than 3 hourly, from all doses of methadone (including regular doses).

Sometimes methadone is added alongside an existing opioid as they can act in synergy (regimes include 2.5mg or 5mg bd).

Pharmacokinetics

Methadone is a highly lipophilic drug and with repeated use it forms an extensive tissue reservoir. This along with being highly protein bound contributes to a long plasma half-life ranging from 8-75 hours. This half life increases with patient age. It is mainly metabolised in the liver and about half of the drug and its metabolites are excreted via the intestines and half by the kidneys. However renal and hepatic impairment do not significantly affect methadone clearance. Its oral bioavailability is 80% however this may range from 40-80%. Onset of action is thought to be within 30 minutes, however patients have reported this to be up to an hour after oral administration^{1,2,3}

Dosage and administration

- Switching to methadone will be under the care of palliative care team in the hospice or acute trust. The previous opioid will be stopped abruptly.
- A dose of methadone $1/10^{\text{th}}$ of the 24 hour oral morphine dose is given as a loading dose (max 30mg) and $1/30$ of the 24 hour oral morphine dose (up to a maximum of 30mg) will be prescribed on a 3 hourly prn basis.
- The patient may take a regular dose every **3 hours prn. Peak concentration may take up to 3 hours hence 3 hourly prn limit.**
- During the titration period (3 hourly methadone prn), if the patient has pain in between the 3 hourly doses, they may be given an alternate opioid or NSAID or paracetamol.
- By days 5 or 6, if the dosing has become stable, the amount of methadone taken over the previous 48 hours is noted and converted into a regular b.d. dose, with the provision for extra doses, that are $1/6^{\text{th}}$ the total daily dose, to

be available 3 hourly prn. **Please note that some patients may require a lower prn dose e.g. 1/10th of the total daily dose.**

- If prn medication is still required, increase the dose of methadone by ½ to 1/3 every 4 to 6 days.

Example: For a patient on morphine 200mg per 24 hours, loading dose is 1/10th ie 20mg, initial 3 hourly prn is 200mg/30 =7mg (rounded). By day 6, if taking 120mg of methadone in 48 hours then the b.d. dose is 120mg/4 =30mg, with 60mg(daily dose)/6 = 10mg as a prn dose.

Example: For a patient on morphine >600mg per 24 hours. The initial loading dose is 30 mg, and 3 hourly prn is 20mg.

Synergy of methadone with a concurrent opioid

There is increasing evidence anecdotally and in animal models that methadone can work in synergy with other strong opioids.^{5,6}

The following regime is suggested and agreed by consultant consensus:

- Add 5mg methadone b.d. along side the regular long acting opiate.
- Increase as necessary on a weekly basis

Conversion to subcutaneous route

As stated previously oral bioavailability of methadone ranges from 40-80 %. Traditionally a conservative conversion ratio has been used of 2:1 from the oral to subcutaneous route. However some centres are now using 2/3 of the oral dose subcutaneously.^{1,7}

Example: Total 24 hour dose of oral methadone is 40mg therefore subcutaneous dose is 20mg. The prn dose **may be up to** 1/6 of the total 24 hour subcutaneous dose, i.e. 3mg in this case.

Cautions in Use

Careful observation of the Respiratory Rate must be maintained – see Toxicity

The subcutaneous infusion should not be started within 12 hours of taking the last oral dose of methadone, although prn dosing should be available.

Subcutaneous methadone can irritate the skin. It should therefore be diluted as much as possible in saline. If other drugs are to be used in the same syringe driver, compatibilities should be checked. The addition of dexamethasone 0.5mg may be helpful.

Toxicity

Methadone has a similar side effect profile to other strong opioids including constipation, nausea, sedation, cognitive impairment and hallucinations. The most important side effect not to miss is **respiratory depression**.^{1,8}

Contraindications

Hypersensitivity. No other absolute contraindications provided it is carefully titrated against the patient's pain.²

Monitoring

Renal and hepatic impairment do not affect methadone clearance. Monitor for respiratory depression as above.

The CHM recommends that patients with the following risk factors for QT interval prolongation are carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or taking drugs which can prolong the QT interval; patients requiring more than 100mg methadone daily should also be monitored.

Drug Interactions – key importance for primary care prescribers

Amitriptyline, SSRIs, cimetidine, macrolide antibiotics, ciprofloxacin, ketoconazole and fluconazole will **increase plasma methadone**. Carbamazepine, phenytoin, phenobarbital, risperidone and rifampicin will **decrease plasma methadone**. Methadone increases zidovudine levels.

Ensure you check for interactions before stopping or starting other medication as reactions are clinically significant.

Side Effects

Nausea, vomiting (especially at initiation), constipation and drowsiness, respiratory depression, hypotension and muscle rigidity. Other side effects include difficulty with micturition, ureteric or biliary spasm, dry mouth, sweating, headache, vertigo, dysphoria.

Cost

Methadone oral solution 1mg/ml. £2.08 per 100ml.

Injection 50mg/ml amp £1.38 per 1ml amp.

References

1. Guidelines for use of methadone for cancer pain. www.palliativedrugs.com newsletter. March 2004.
2. Palliative care formulary 2nd ed
3. Stannard C, Booth S. Pain. Churchill Livingstone 3rd Ed London 2004
4. Manfredonia JF. Prescribing methadone for pain management in end of life care. JAOA Vol 105 No 3 March 2005 18-21
5. Bolan EA, Tallarida RJ, Pasternak GW. Synergy between mu opioid ligands: evidence for functional interactions among mu opioid receptor subtypes. J Pharmacol Exp Ther. 2002 Nov;303(2):557-62
6. Mercandante S, Villari P, Ferrera P, Casuccio A. addition of a second opioid may improve opioid response in cancer pain. Support Care Cancer. 2004 Nov;12(11):762-6
7. Guidelines for the use of methadone in palliative care. Compton Hospice Clinical guidelines group December 2003
8. Keen JC. Methadone in palliative care guidelines. St Columba's Hospice Edinburgh
9. British National Formulary 72. March 2017. P21
10. Twycross R and Wilcock A. Editors-in-Chief. Palliative Care Formulary (PCF5). Palliativedrugs.com 5th Edition Nottingham 2014.

NALOXONE: Use in Management of Opioid Induced Respiratory Depression

Discuss patient with a palliative medicine consultant when using this guideline.
Patients need to be kept under continuous supervision.

Description:

Opiate antagonist. Reversibly blocks access to opiate receptors and displaces opiate agonists due to its higher affinity.

Formulation:

400 micrograms/ml injection (1ml ampoule)

Indications:

- Treatment of acute opioid overdose (not included in guidelines – refer to BNF)
- Reversal of life-threatening respiratory depression associated with medicinal opiate use: Respiratory rate <8 per minute and oxygen saturations <85%, cyanosis, patient barely rousable.

Management:

- If respiratory rate ≥ 8 , oxygen saturations >85%, no cyanosis and patient easily rousable: **PATIENT DOES NOT HAVE LIFE-THREATENING RESPIRATORY DEPRESSION.** Consider other causes of respiratory dysfunction e.g. P.E., pneumonia, is the patient dying? Watch and wait. Omit next regular dose of opiate / review patch or syringe driver dose. Closely monitor the patient ensuring adequate hydration and oxygenation.
Take bloods for FBC, U+Es, LFTs and calcium.
- If respiratory rate <8 and oxygen saturations <85%, cyanosis and patient not easily rousable:
TREAT FOR LIFE-THREATENING RESPIRATORY DEPRESSION.
- Stop / reduce background opiate particularly if it has a long half-life e.g. patches / MR preparations.
- Oxygen.
- Cannulate.
- Aim to give dose of naloxone to correct respiratory depression but ensure on-going adequate analgesia.
- Dilute 400 micrograms of naloxone (1 ampoule) to 10mls with 0.9% sodium chloride in a 10ml syringe. (40micrograms/ml)
- Administer 20micrograms naloxone (0.5mls) as a slow IV bolus.
- Repeat 20micrograms (0.5mls) every 2 minutes until respiratory rate is above 8. Note dose is titrated to respiratory rate NOT to conscious level.
- Flush the cannula with 0.9% sodium chloride after every dose administered.
- A maximum of 100-200micrograms (approximately 1.5-3micrograms per kg) is usually sufficient to produce an optimum respiratory response while maintaining adequate analgesia.
- If little or no response consider other causes e.g. sedative medications like benzodiazepines, intra-cranial event.
- When patient more stable send bloods for FBC, U+Es, LFTs and calcium.

- Continue to monitor patient closely. Duration of action of naloxone is 15-90 minutes; therefore repeated doses may be required. Suggest repeating RR every 15 minutes for first hour, then every 30 minutes for next 2 hours then hourly.

NB The intravenous route has the fastest onset of action (2-3 minutes) but if not feasible the IM route can be used (onset of action 2-5 minutes). If intravenous access is not possible can give IM but longer onset of action may require higher doses. Suggest starting with 100micrograms.

Prolonged or Recurrent Respiratory Depression Requiring Repeated Naloxone Doses:

- Commence a continuous intravenous infusion of naloxone.
- Add 1mg of naloxone (2.5 ampoules of 400 micrograms/ml) to 100mls 0.9% sodium chloride to give a concentration of 10 micrograms/ml.
- To calculate the dose requirement per hour: total all naloxone bolus doses given and divide by number of hours these were administered over. Start the infusion at 50% of this calculated hourly rate.
E.G. if required 150micrograms over 1.5 hours.
 $150/1.5 = 100\text{micrograms/hr}$
 $100/2 = 50 \text{ micrograms/hr}$
 $50/10 = 5\text{mls/hr}$
- Adjust the infusion rate to maintain respiratory rate >8. Do not adjust to conscious level as total antagonism will cause a return of severe pain.

Adverse effects of naloxone:

If naloxone given in higher than recommended doses:

- Acute opiate withdrawal syndrome
Abrupt return to pain, anxiety, agitation, nausea and vomiting.
- Increased sympathetic nervous stimulation and cytokine release.
Tachycardia and hypertension, and rarely; arrhythmias, pulmonary oedema and cardiac arrest.

NB Particular attention should be paid to elderly patients with a background of cardiovascular disease or those receiving potentially cardio-toxic medications.

Considerations:

- Please be aware that doses appropriate for acute opiate overdose may be too large for treating respiratory depression in those on long-term opioids or palliative patients.
- The effect of naloxone may be shorter than long-acting opiates e.g. methadone and fentanyl. (naloxone half-life 1 hour, duration of action 15-90

minutes). In the case of buprenorphine higher doses of naloxone are likely to be needed as buprenorphine has higher receptor affinity.

- No need to alter dose with renal failure.
- Naloxone may not be appropriate in patients who are dying.

References:

BNF.

Twycross R, Wilcock A. Palliative Care Formulary (5th edition) 2014.

<http://www.palliativecareguidelines.scot.nhs.uk/> Scottish Palliative Care Guidelines – Naloxone.

Medicines.org.uk.

Miaskowski C et al. (2008) Principals of analgesic use in the treatment of acute pain and cancer pain (6e). American Pain Society, Skokie, Illinois, p.31.

Pilgrims Hospices in East Kent: Guidelines for the use of naloxone in Buprenorphine Overdose and Iatrogenic Opiate Overdose. 2014.

NHS England Patient safety alert 20/11/14: Risk of distress and death from inappropriate doses of naloxone in patients on long-term opioid/opiate treatment.

Manfredi P, Ribeiro S, Chandler S, et al. Inappropriate use of naloxone in cancer patients with pain. J Pain Symptom Manage 1996;11:131–134.

Electronic Medicines Compendium. www.medicines.org.uk/naloxone accessed at [http://www.medicines.org.uk/emc/medicine/21095/SPC/Naloxone+400+micrograms+ml+solution+for+Injection+\(hameln\)/](http://www.medicines.org.uk/emc/medicine/21095/SPC/Naloxone+400+micrograms+ml+solution+for+Injection+(hameln)/)

GUIDELINES FOR THE USE OF METHYLNALTREXONE

Indication:

In opioid-induced constipation in advanced illness in patients receiving palliative care who are unresponsive to usual the usual stimulant and softening laxative measures, on the recommendation of a palliative care specialist. Laxatives tried should include lactulose, senna, docusate sodium, sodium picosulfate, danthron, laxido.

Consider if

- Titration & switching of laxatives & rectal measures is ineffective or inappropriate *and*
- Opioids are thought to be a significant cause of their constipation.

Pharmacology & Pharmacokinetics

Methylnaltrexone blocks opioids action on the gastrointestinal tract (a 'mu receptor antagonist'). However, it does not penetrate the blood brain barrier, so should not interfere with their analgesic effect.

Pharmacokinetic properties

- Absorption: Peak plasma concentration 30mins after SC injection
- Distribution: Does not readily cross the blood brain barrier
- Metabolism and elimination: Around 1/3 is metabolised to either inactive or partially active compounds. These, plus the un-metabolised parent drug, are predominantly renally excreted. Half-life is ~8 hours.

Therefore dose reduction is advised in renal impairment, and caution is advised with severe renal and severe hepatic impairment – dose adjustment below.

Discuss use in such patients with a consultant.

Dose and Administration

Continue regular laxatives alongside methylnaltrexone

Prescribe subcutaneously once & review response before giving further doses. 25% of patients usually respond within 30 minutes and a further 25% within 4 hours.

Dose is according to weight (if in doubt, use lower dose):

- Give **8mg** on alternate days if **38-61kg** and assess.
- Give **12mg** on alternate days if **62-114kg** and assess
- Outside these ranges dose at 0.15mg/kg

If patients are very obese start at 12mg dose and assess response. Consult palliative care consultant for advice.

Consider a lower test dose with colostomy, diverticulosis, or faecal impaction

The intervals between administrations can be varied but should not be given more than once a day.

Cautions in use

Reduce dosage by half in severe renal failure. Not recommended in end-stage renal impairment requiring dialysis. No dosage adjustment is required in mild to moderate hepatic impairment although it has not been studied in severe impairment.

Consider hyoscine butylbromide 20mg SC in case of severe colicky pain

Contraindications

Known or suspected mechanical gastrointestinal obstruction
When constipation is unrelated to opioid use
Known allergy to methylnaltrexone or the product constituents

Monitoring & Adverse effects

Bowel action can occur quickly (within 30-60mins) and can be diarrhoea, so consider incontinence sheets, commode at bedside if appropriate.
If giving via a SC line, flush with sodium chloride 0.9%. Rotate site if reaction occurs.

Adverse effects:

Very common (>1 in 10) Abdominal pain, nausea, flatulence, diarrhoea
Common (>1/100 – 1/10) Dizziness, injection site reactions

Drug interactions

No significant interactions have been noted to date.

Cost

£ 21 for 1 ampoule of 12mg in 0.6ml

References

1. Summary of product characteristics (see <http://emc.medicines.org.uk/>)
2. Thomas J et al *Methylnaltrexone for opioid-induced constipation in advanced illness*.
3. N Eng J Med 2008; 358: 2332-43
4. <http://www.palliativedrugs.com/opioid-antagonists> (main text and donated guidelines) accessed 8.12.2008
5. Further information: Methylnaltrexone (Relistor) UKMi London New drugs Group APC/DTC Briefing Document July 2008

GUIDELINES FOR THE USE OF METHYLPHENIDATE

This should be initiated by or after discussion with a specialist in palliative care.

Indications

Methylphenidate is a CNS stimulant used in palliative care for opioid related sedation, fatigue and depression (sometimes in combination with other antidepressants).

Pharmacology

Its mechanism of action is by blockade of pre-synaptic dopamine reuptake.

Pharmacokinetics

The immediate release formulation has an onset of action of 20 to 40 minutes and duration of action of 3 to 6 hours. It is normally given BD, on waking and at lunchtime, to reduce any potential for insomnia.

Dosage and administration

Start at 5mg BD (on waking and lunchtime) or 2.5mg BD if particular concern about side effects.

Titrate up by 5mg BD steps every 3 days, titrating benefit against any side effects, to a maximum dose of 20mg BD. Occasionally higher doses are required (e.g. 30mg BD, 20mg TDS).

Cautions

Psychosis, significant cardiovascular disease.

Interactions

May antagonise anti-epileptic effect of phenytoin and action of anti-hypertensives. Inhibits metabolism of TCAs and warfarin.

It is normally well tolerated (better than TCAs).

Side effects

Very common (>10%) include nervousness and insomnia (responds to dose reduction).

Common (>1% but <10%) include headache, dizziness, palpitations, arrhythmias, hypertension, nausea and vomiting, anorexia, dry mouth, rash, pruritis, fever, arthralgia.

Monitoring

For adverse effects eg:

anxiety, agitation, sleeplessness; hypo/hypertension, arrhythmias, palpitations;

For drug interactions with methylphenidate particularly: warfarin and phenytoin

Cost and supply

It is a controlled drug (CD)

Methylphenidate tablets 5mg – 30 tabs £3.44 10mg – tabs £7.17.

Ritalin 10mg (scored) 30 tabs £6.68

References

Palliative Care Formulary 6th Edition
British National Formulary 72 March 2017

GUIDELINES FOR THE USE OF BUCCAL MIDAZOLAM

Indications

Midazolam is a short acting benzodiazepine – it can be given by the buccal route as an alternative to rectal diazepam for patients prone to prolonged generalised seizures (lasting longer than 5 minutes), clusters of seizures or status epilepticus. Rectal diazepam whilst licensed can be practically difficult to administer, socially unacceptable and have variable bio absorption. Midazolam is as effective as rectal diazepam, is absorbed rapidly through the buccal cavity, and has practical advantages of ease and social acceptability in administration.

Pharmacology & Pharmacokinetics

The solution is placed against the gums and cheeks for best absorption. If swallowed absorption of the solution may be less effective.

Dosage and administration

A preparation of Midazolam specifically intended for the buccal route is available from a variety of specials manufacturers. Buccolam oromucosal solution is a prefilled syringe licensed product for under 18 year olds, but not currently licensed for over 18s.

The dose for adults and children over 10 years is 10mg.

Administration is as per the SPC and patient information leaflet

<https://www.medicines.org.uk/emc/product/7460/smpc>

Contraindications

Known hypersensitivity to the drug or any excipients.

Acute narrow angle glaucoma.

Monitoring & Adverse effects

The most common reported side effect is drowsiness; in some cases this may be severe. All patients receiving midazolam are likely to be drowsy for several hours after administration. Agitation and disorientation may occur but are rare.

No specific monitoring is necessary.

Drug interactions

Erythromycin, other macrolides and cimetidine inhibit metabolism of midazolam. This **may** result in prolonged duration of sedative side effect.

Cost

Buccolam 10mg/2ml oromucosal solution prefilled syringe £22.88

References

1. BNF 72 pg 310
2. Palliative Care Formulary 6th Edition

GUIDELINES FOR THE USE OF OCTREOTIDE

Indications

The use of octreotide in palliative medicine is frequently beyond licence and indications include:

- Symptoms associated with unresectable/metastatic hormone secreting tumours, e.g. carcinoid, glucagonomas, insulinomas.
- Malignant bowel obstruction/high volume/intractable vomiting.
- Severe tumour related secretions.
- Intractable diarrhoea.
- High output gastrointestinal fistulae.
- Malignant ascites
- Bronchorrhoea (death rattle).^{1,2}

Pharmacology

Octreotide is a long acting-synthetic somatostatin analogue.^{1,2,3} Somatostatin is an inhibitory hormone found throughout the body. It suppresses the secretion of serotonin and endocrine secretions of the pancreas, stomach and intestine, including glucagon, gastrin, insulin, vasoactive intestinal peptide (VIP) and secretin. In type I diabetes mellitus octreotide decreases insulin requirements, however in type II diabetes mellitus octreotide suppresses both insulin and glucagon release and plasma glucose levels therefore remain unchanged or only slightly raised.¹ The inhibition of gut hormones by octreotide reduces splanchnic and portal blood flow,^{1,3} gastrointestinal motility, gastric, pancreatic and small bowel secretions and increases water and electrolyte absorption.^{1,2,3} Octreotide also has a direct anticancer effect on solid tumours of the gastrointestinal tract, probably by blocking the action of epidermal growth factor (EGF) thus prolonging survival.³

Pharmacokinetics

Octreotide is poorly absorbed from the gastrointestinal tract. It is completely and rapidly absorbed after subcutaneous injection and is 65% plasma protein bound. It has inactive metabolites and is mainly excreted unchanged (32%) by the kidney.³ The onset of action is 30 minutes. Time to peak plasma concentration 30 minutes subcutaneously. Plasma half life 1.5 hours subcutaneously. Duration of action 8 hours.^{1,2}

Dosage and administration

Octreotide is administered as subcutaneous bolus injections, bd to tds, or as a continuous subcutaneous infusion (CSCI). The dose varies according to indication and should be titrated according to response. The usual range is 50 – 1500 micrograms daily, although higher doses are occasionally used depending on the patient. Once improvement of the symptom is achieved reduction in dose can be tried.^{1,2}

Continuous Subcutaneous Infusion

When given by CSCI 0.9% sodium chloride is used as the diluent. It normally mixes well depending on concentrations with dexamethasone (<1mg), midazolam, haloperidol, diamorphine, oxycodone, morphine, hyoscine butylbromide and

metoclopramide. Precipitation may occur with cyclizine.^{1,2,3} If more than two drugs are to be mixed in the same syringe please seek further specialist advice.

Cautions

Insulinoma (may potentiate hypoglycaemia). In diabetes mellitus insulin or oral hypoglycaemic requirements may be reduced.

Monitoring

Clinical response (e.g. volume/frequency of vomiting/diarrhoea)

Drug Interactions

Octreotide has been reported to reduce the intestinal absorption of ciclosporin and delay the absorption of cimetidine. In diabetes mellitus insulin or oral hypoglycaemic requirements may be reduced.^{1,2,3} Concomitant administration of octreotide and bromocriptine increased the availability of bromocriptine.³ Limited data indicates that it may decrease the metabolic clearance of compounds known to be metabolised by cytochrome P450. Use with caution with carbamazepine, digoxin, warfarin and terfenadine.^{1,2,3}

Side Effects

The most common side effects are dry mouth, gastrointestinal disturbances including anorexia, nausea, flatulence (due to reduction in oesophageal sphincter tone), vomiting, abdominal pain, steatorrhoea (due to the inhibition of pancreatic enzyme secretion) and gallstone formation (due to biliary stasis).^{1,2} These may be reduced by timing the injections between meals or at bed time.³ Steatorrhoea may be overcome by the use of pancreatic enzyme supplements. Rarely hyperglycaemia has been reported with chronic administration and hypoglycaemia has also been reported. Rarely pancreatitis has been reported shortly after administration. Bolus injection is painful but less if the vial is warmed to room temperature.^{1,3}

Costs:

100 microgram £6.53 per amp.

1mg/5ml multi-dose vial £ 69

Depot preparations

Depot preparations of octreotide 10 – 30mg given every 4 weeks are available. Alternatively lanreotide (Somatuline[®] LA) 30mg given every 2 weeks (sometimes every 7 – 10 days) and lanreotide (Somatuline[®] Autogel) 30 – 90mg given every 4 weeks could be used. In palliative care these long acting preparations are generally used when symptoms have first been controlled with subcutaneous octreotide. The most common problems for which they are used are in patients with chronic intestinal fistulae or intractable diarrhoea. They are given by deep intramuscular injection into the gluteal muscle.

Patients switching over to the depot medication may need to continue to receive subcutaneous octreotide for about two weeks and some patients may require additional rescue octreotide for up to 2 – 3 months because of the time to reach steady state lanreotide levels.³

References

- 1 Palliative Care Formulary 6th Edition
- 2 Octreotide in www.palliativedrugs.com
- 3 Octreotide CCO formulary

GUIDELINES FOR THE USE OF OLANZAPINE

Olanzapine has been used in palliative patients where its receptor activity and side effect profiles have been deemed to be beneficial over Levomepromazine. It is a potent D₁, D₂, D₃, D₄, 5HT_{2A}, 5HT_{2C}, 5HT₃ and 5HT₆ antagonist with activity at ACh, α₁-adrenergic and H₁ receptors.

Indications

Nausea and vomiting as a third line choice:

- For patients in whom Levomepromazine has been too sedating
- Where stimulation of appetite may be a useful side effect

Dosage and administration

- It comes in tablet, oro-dispersible tablet and an IM injectable form (unlicensed for s/c route but use supported by case series)
- As an anti-emetic start with 1.25 to 2.5mg stat, prn and at night
- If necessary increase to 5mg at night, maximum 5mg bd
- Time to peak plasma concentration 5-8 hours
- Duration of action about 12-48 hours. Plasma half-life 34 hours; 52 hours in the elderly. Unchanged in renal or hepatic impairment.

How to use:

See palliative care formulary for more information **and discuss with a palliative care specialist.**

Cautions in Use

For full list, see SPC.

Increased mortality in patients with dementia. Over-sedation has occurred with higher doses and with concomitant use of benzodiazepines. Significant cardiovascular disease.

Contraindications

As for antipsychotics, see BNF

Monitoring

No specific monitoring is required

Drug Interactions

See BNF

Side Effects

Sedation, extra-pyramidal, as for antipsychotics.

Cost Generic tablets x 28 2.5mg £5.21; 5mg x 28 £11.38.

Orodispersible 5mg x 28 tablets £1.79;

Injection 10mg vial £43

Reference

Palliative Care Formulary 6th Edition

GUIDELINES FOR THE USE OF ONDANSETRON & GRANISETRON

5HT₃ antagonists were developed to counter highly emetogenic stimuli such as platinum based chemotherapy and certain radiotherapy regimes. They are also successfully used as 3rd or 4th line anti-emetics for intractable vomiting where usual approaches have failed.

Indications

- Nausea and vomiting in a palliative situation where other antiemetics including metoclopramide, haloperidol, cyclizine, levomepromazine and dexamethasone have not worked.
- Cholestatic or uraemic itch

Dosage and administration

- Ondansetron 8mg bd PO or SC (or 16mg over 24 hours by syringe driver)
- Granisetron 1-2mg od PO or SC
- Trial for 3 days – continue if effective, stop if not
- Typically they are used in combination with an antiemetic with multiple sites of activity eg Levomepromazine or Olanzapine +/- Dexamethasone
- Duration of action – Ondansetron 12 hours, Granisetron 24 hours

How to use:

See palliative care formulary for more information **and discuss with a palliative care specialist.**

Cautions in Use

Reduce dose of Ondansetron to 8mg in moderate or severe hepatic impairment. For full list, see SPC.

Contraindications

Not to be used intravenously with IV metoclopramide – risk of arrhythmia.

Monitoring

No specific monitoring is required

Drug Interactions

See BNF

Side Effects

Very common – headache. Common includes - constipation. See BNF for full list.

Cost

Ondansetron

Oral - 4mg, 10 tabs £1.88, 8mg, 10 tabs £35

Injection – 2mg/ml – 2ml £5.70, 4ml £11

Granisetron

Oral – 1mg 10 tabs £51.20

Injection – 1mg/ml, 1ml £1.60, 3ml £4.80

Reference

Palliative Care Formulary 6th Edition

(excluding granisetron patch – information from MIMS December 2013 and SPC updated October 2013)

GUIDELINES FOR THE USE OF QUETIAPINE

Quetiapine has been used in palliative patients where its receptor activity and side effect profiles have been deemed to be beneficial over other antipsychotics. It is a (least of all anti-psychotics) D₂, D₃, 5HT_{2A}, 5HT_{2C} antagonist with activity at ACh, α_1 and α_2 -adrenergic and H₁ receptors.

Indication

Delirium in Parkinson's Disease and related conditions:

Dosage and administration

- It comes in tablet form (we advocate immediate release not MR) that can be crushed if needed.
- For delirium start at 12.5mg BD and if needed increase in 12.5 to 25mg increments. Balancing benefits and harms, reduce dose where possible if Parkinsonism increases.
- Mean effective dose 40 to 100mg daily
- Time to peak plasma concentration 5-8 hours
- Duration of action about 12-48 hours. Plasma half-life 34 hours; 52 hours in the elderly. Unchanged in renal or hepatic impairment.

How to use:

See palliative care formulary for more information **and discuss with a palliative care specialist.**

Cautions in Use

For full list, see SPC.

Increased mortality in patients with dementia. Over-sedation has occurred with higher doses and with concomitant use of benzodiazepines. Avoid with significant cardiovascular disease.

Contraindications

As for antipsychotics, see BNF

Monitoring

No specific monitoring is required

Drug Interactions

Increased concentration by CYP3A4 inhibitors (eg azole antifungals and macrolide antibiotics).

Reduced concentration by enzyme inducers (eg carbamazepine and phenytoin).

See BNF

Side Effects

Sedation, extra-pyramidal, as for antipsychotics.

Cost (28 days)

25mg x 60 tablets £ 38 (BNF price) £1.11 (drug tariff price)

Reference

Palliative Care Formulary 6th Edition