Yorkshire Palliative Medicine Clinical Guidelines Group

Guidelines on the use of strong opioids

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Overall objective: to provide guidance on the use of strong opioids in patients with cancer pain

Introduction

Strong opioids are used to treat moderate to severe cancer pain. Although morphine is the benchmark strong opioid there are various alternative strong opioids available.
These guidelines are intended to provide the most recent evidence for the efficacy, side effects and benefits of the commonly available strong opioids used in palliative care in the UK. It should be remembered that on switching from one strong opioid to another, patients may experience opioid withdrawal symptoms.

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Morphine/Diamorphine

Use morphine as first line strong opioid orally and diamorphine as parenteral form (Hanks 2001).

Exceptions

- Morphine allergy (rare) or severe itch
- In the presence of significant renal impairment alfentanil, fentanyl and buprenorphine are safer. Methadone can be used (but has complex pharmacology) and hydromorphone and possibly oxycodone have less toxic metabolites.
- Consider transdermal fentanyl or buprenorphine when oral route difficult or there are concerns about absorption and parenteral route not appropriate
- Consider alternative opioid when there are issues of patient acceptability of morphine

Alfentanil

Synthetic derivative of fentanyl.
Preparation: injection only
Onset of action: <2 min iv, < 5 min IM
Time to peak plasma concentration: 15 min IM
Duration of action: 10 min iv, 1 hour IM

Pharmacokinetics of single iv doses (Scholz 1996)

	Fentanyl	Alfentanil
Onset of action (min)	1.5	0.75
Plasma halflife (min)	220	100
Duration of action (min)	30 - 60	10

Dose conversion ratios:
SC diamorphine to SC alfentanil – give 1/10 of dose
PO morphine to SC alfentanil – give 1/30 of dose
Metabolism – in liver by CYP3A4 to inactive compounds – dose reductions may be necessary in patients with severe liver impairment but not in renal failure
(Twycross et al 2002)
No local complications after subcutaneous use in children (Ozcengiz 1996).
Similar side effect profile to morphine.

Advantages

Higher speed of onset and effectiveness of analgesia after PCA bolus compared to morphine (Ngan Kee 1999).

One study suggested that long term use may be limited by tolerance (Hill 1992) but no evidence of tolerance in another (Schragg 1999).
4 patients with known impaired renal function agitated on CSCI diamorphine, settled rapidly on changing to alfentanil (Kirkham 1995)

Summary

- Consider subcutaneous use in patients with renal failure who require a parenteral strong opioid, particularly in whom there is evidence of morphine neuro-excitability.

- Consider stat injections for painful procedures

Buprenorphine - transdermal

Mu agonist, weak delta agonist and Kappa antagonist.
Matrix patch, therefore can be cut if necessary.
No clinically relevant ceiling dose with the transdermal preparation.
No dose adjustment needed in renal failure (Budd 2002).
Avoid concomitant use with MAOIs.
May need high doses of naloxone in overdose.
Clinically effective after 12-24 hours so continue with current medication for 12 hours after the application of the patch
Lowest patch is 35mcg/hour which is equivalent to 30-60mg oral morphine in 24hours

Comparative analgesia

Superior to placebo (Bohme 2002, Radbruch 2003).

Advantages

Buprenorphine is safe in renal failure (Budd 2002).
Narrower dosing intervals to fentanyl and lower starting patch strength.
No good quality studies to show better side effect profile.

Summary

- Consider use in patients with stable pain and renal failure.

- Consider if a low strength transdermal system is needed.

- Consider in patients who have swallowing difficulties for whom parenteral treatment is not appropriate

- Consider in patients where there is concern about absorption of oral preparations

- May be useful if poor compliance with oral medication

Fentanyl – transdermal

Pure mu agonist in reservoir patch (i.e should not be cut or partially covered)
Conversion from oral morphine - see appendix 1
Lowest patch is 25mcg/hour which is equivalent to 30-135mg oral morphine in 24 hours
Approximately 10% of patients develop erythema and less than 1% localised pruritis, oedema and papules (Donner 1998, Radbruch 2001).
Some patients (14-28%) experience poor pain control on the day before the patch is changed (i.e 48-72 hours after application) but experience intolerable side effects (particularly drowsiness) if the patch strength is increased. It is appropriate to change the patch every 48 hours in such patients (Donner 1998, Radbruch 2001).
For use in moribund patients see appendix 2.

Comparative analgesia

Analgesic efficacy similar to morphine (Sloan 1998, Donner 1998, Radbruch 2001, Allan 2001)

Advantages

Safe use in renal failure
Less constipation and laxative use than morphine (Donner 1998, Ahmedzai 1997, Rabruch 2000)
Sleeping patterns - possible reduction in daytime drowsiness (McNamara 2002)
Transdermal delivery system preferred by some patients

Summary

- Consider in patients who develop intractable constipation despite optimal laxative treatment
- Consider in patients with ‘stable pain’ who have renal impairment
- Consider in patients who have swallowing difficulties for whom parenteral treatment is not appropriate
- Consider in patients where there is concern about absorption of oral preparations
- May be useful if poor compliance with oral medication
- Possible reduction in daytime drowsiness

Fentanyl - Oral Transmucosal Fentanyl Citrate

Fentanyl in a hardened sweetened matrix
50% bioavailability, 25% absorbed through buccal mucosa and 25% via the gut
Onset of action less than 30 minutes
Duration of action 1-3 hours
Optimal dose is determined by titration and cannot be predicted by a patient's regular dose of opioid (Christie 1998, Poutenoy 1999)
Clinical experience shows patients with xerostomia may have difficulty using the lozenge

Comparative analgesia/advantages

Effective analgesic (Fine 1991, Christie 1998, Portenoy 1999, Payne 2001, Coluzzi 2001)
May have a faster onset of action than oral morphine (Fine 1991, Christie 1998)

Summary

- Consider use in patients with incident pain and a good performance status

Fentanyl - sublingual

Fentanyl and sufentanil are highly lipid soluble and have good sublingual bioavailability and a rapid onset of action.

Case reports and series have shown sublingual fentanyl/sufentanil to be effective analgesics with quick onset of action and short duration. Problems with bitter taste, dry mouth and difficulty retaining volumes over 1ml may occur (Kunz 1993, Gardner-Nix 2001, Zepetella 2001).

See appendix 3 for use in incident pain.

Hydromorphone

Mu receptor agonist.
Potency 5 – 10 times oral morphine
Immediate release (lowest dose IR preparation is 1.3mg) and 12 hour slow release capsules available, can be opened if swallowing problems.
Parenteral form not routinely available but can be obtained from Martindale (oral to sc hydromorphone conversion 1:3, range 2.5-5.0)
1.3mg oral hydromorphone is approximately equivalent to 10mg oral morphine

Comparative analgesia

Analgesic efficacy appears to be similar to oral morphine (Moriarty 1999, Dunbar 1996, Coda 1997, Miller 1999, Collins 1996)

Advantages

Less confusion (Bruera 1995)

Lower incidence of itch (Katcher 1999, Chaplan 1992).

Use in renal failure. Evidence suggests safety as main metabolite, hydromorphone-3-glucuronide thought not to have pharmacological activity (but levels do increase in renal failure) (Lee 2001). However, 2 papers cite case studies suggesting otherwise. (Babul 1995, Fainsinger 1993).

Summary

- Consider in patients who develop morphine related itch, confusion or who have impaired renal function

Methadone

Mu and delta receptor agonist.
Evidence of NMDA receptor antagonist in vitro (Ebert 1998, Oxenham 1998)
Oral tablets and liquid available
SC infusion possible (Mathew 1999) (conversion from oral to subcutaneous dose 2:1 (Dickman 2002))
Long and variable half life and high volume of distribution so problems with accumulation
Drug interactions – contraindicated with MAOIs, clearance reduced by amitriptyline and cimetidine, increased metabolism by carbemazepine, phenobarbital, phenytoin, rifampicin
Metabolites inactive so may be useful in renal failure

Various schemes for conversion from oral morphine are available (Blackburn 2002, Mercadande 2001, Morley 1998, Nauck 2001, Scholes 1999, Tse 2003). An example is shown below.

Scheme suggested by Morley and Makin (1998)

- Stop morphine abruptly
- Prescribe a dose of methadone that is 1/10th the 24hour PO morphine dose (upto a maximum of 30mg)
- Allow the patient to take the prescribed dose q3h prn
- On day 6, the amount of methadone taken over the previous two days is noted and converted into a regular q12h dose, with provision for a similar or smaller dose q3h prn
- If prn medication is still needed, increase the dose of methadone by ½ - 1/3rd every 4-6 days

Advantages

Evidence available to support use of methadone in patients whose pain is incompletely controlled by oral morphine or where the dose of morphine required to provide adequate analgesia causes unacceptable side effects (thought to be due to accumulation of morphine metabolites). Case reports suggest methadone may be helpful in 'difficult pain' with neuropathic elements (Crews 1993, Leng 1994, Makin 1998, Manfredi 1997, Mercadante 2001, Zylicz 1997)

No convincing evidence to suggest benefits in side effect profile compared to morphine except due to dose reduction in overall opioid requirement.

Summary

- Consider in patients who have difficult pain to control with oral morphine particularly where a neuropathic mechanism is implicated
- Widespread use is limited by its complex pharmacology.

Oxycodone

Mu and kappa agonist
Potency 1.5-2 x that of oral morphine
Immediate release (capsules and liquid 1mg/ml and 10mg/ml), sustained release 12-hour tablets, and injection (10mg/ml)
Oral to parenteral 2:1 (as recommended by manufacturer)
Biphasic release system
Use with caution in renal failure (increased concentrations of noroxycodone, reduced clearance and increased sedation) (Kirvela M 1996, Kaiko R 1996)
10mg of oral morphine is approximately equivalent to 5mg oral oxycodone

Comparative Analgesia

Analgesic efficacy appears to be similar to morphine (Heiskanen 2000, Hagan 1997, Mucci-LoRusso 1998, Bruera 1998, Parris 1998)

Advantages

Suggestion of fewer hallucinations (in 2 patients) and less cognitive impairment (Gagnon 1999, Mucci-LoRusso 1998)
Possibly less nausea and vomiting but increased constipation (Heiskanen 2000, Maddocks 1996)
Less itch than oral morphine (Mucci-LoRusso 1998)
Evidence of benefit over placebo in diabetic neuropathy and post herpetic neuralgia (but no studies comparing to morphine or co-analgesics) (Watson 1998, Gimbel 2003)

Summary

- Consider in patients with morphine related delirium/cognitive impairment, nausea and vomiting and itch

Appendix 1 Opioid conversions

To convert from oral morphine to

Oral hydromorphone (mg)	Divide by 7.5
Oral oxycodone (mg)	Divide by 2
TD Fentanyl (mcg/hr)	Divide by 3.6 (and choose nearest patch strength)
TD Buprenorphine (mcg/hr)	Divide by 1.7 (and choose nearest patch strength)
Subcutaneous diamorphine (mg)	Divide by 2 or 3
Subcutaneous alfentanil (mg)	Divide by 20 or 30
Subcutaneous oxycodone (mg)	Divide by 4

Note: Equianalgesic doses may be different from those expected. Most of the evidence is from relatively low dose studies that may not necessarily hold true for all patients. The equianalgesic dose also appears to differ depending on which opioid is given first (Scholes 1998)

Appendix 2 TD Fentanyl in moribund patients

In moribund patients, pain can either be controlled by discontinuing the fentanyl patch and converting to a syringe driver containing diamorphine (remembering to calculate dose allowing for the residual fentanyl following patch removal), or by continuing with the fentanyl patch and adding diamorphine if necessary as a stat dose or via a syringe driver. Pain control has been shown not to be compromised in the dying phase with continued use of the fentanyl patch. (Ellershaw, 2002)

The following is suggested: Continue to change the TD fentanyl every 72 hours and give additional diamorphine prn. Rescue doses of SC diamorphine can be based on the 'rule of 5', ie divide the patch strength by 5 and give as mg of diamorphine (Eg fentanyl 100mch/hr use diamorphine 20mg). If 2 or more doses are required in 24 hours, give diamorphine by CSCI, starting with a dose equal to the sum of the prn doses over the proceeding 24 hours. The prn dose needs to be adjusted to take into account the total opioid dose (ie fentanyl and diamorphine CSCI)
(Based on recommendations from Marie Curie Centre Liverpool and Sir Michael Sobell House Oxford. Recommendations in Palliative Care Formulary, 2nd edition)

Appendix 3 Incident Pain Protocol

Incident pain is defined as pain which comes on as a result of an action or activity (E.g. planned turns, transfers, bathing changing clothes, dressing changes and disimpaction).

Approximate equivalent doses are:
Morphine 10 mg = Fentanyl 100 micrograms = Sufentanil 10 micrograms

Steps of the Incident Pain Protocol

Step	Medication	micrograms SL (50 micrograms/ml)
1	Fentanyl	50 #
2	Sufentanil	25
3	Sufentanil	50
4	Sufentanil	100 *

* A dose of 100 micrograms requires 2 ml of the 50 micrograms/ml preparation, which is a rather large volume to be absorbed at once. It is recommended that it be given in two portions of 1 ml (50 micrograms) each, 10 - 15 minutes apart. The planned activity (dressing change, moving the patient, etc) should wait until 10 - 15 minutes after the second portion.

\# In opioid naïve patients, or frail patients with small body mass, consider starting at 12.5 or 25 micrograms of fentanyl sublingually

Application of the Incident Pain Protocol

1 The short acting opioid (fentanyl or sufentanil) is administered sublingually 10-15 minutes prior to anticipated activity. The patient is asked to try to hold the liquid under the tongue for about 10 minutes if possible without swallowing it.

2 If the initial dose appears to be insufficient, that same dose may be repeated up to two further doses at 10-15 minute intervals. If a given dose is sufficient, the patient will typically appear drowsy 10 - 15 minutes following the dose. If this is not the case, or if the patient experiences discomfort during the planned activity, then repeat doses may be given up to a total of three as stated above.

3 Increasing to the next step of the protocol is undertaken if the maximum number of doses (three) is required to achieve comfort, or is insufficient to achieve comfort with activity. Increasing to the next step cannot be done within one hour of the last dose of fentanyl or sufentanil on the most recent implementation.

4 The Incident Pain Protocol may be used up to hourly prn.

Acknowledgement
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Appendix 4 Slow release oral morphine preparation

One double blind randomised double-dummy crossover study in 85 patients has shown no difference between oral MXL (24 hour duration of action) compared to oral MST (12 hour duration of action) in terms of pain scores, sleep, breakthrough medication and side effects (O'Brien 1997).
However, clinical experience shows some patients do not tolerate MXL as well as MST.

Appendix 5

The use of the following drugs is not routinely recommended in palliative care. The following is for information only

Dextromoromide

Not currently manufactured
Dose equivalence 5mg=15mg oral morphine
Variable absorption, onset of action and clearance
No evidence to support its use for incidence pain (Jones 1996)

Tramadol

Weak affinity for opioid mu receptor, inhibits neuronal re-uptake of noradrenaline and induces synaptic serotonin release (only 30% of analgesic actions antagonised by naloxone)
80% oral bioavailability, half life approximately 6hrs
Metabolised in the liver, renally excreted
Conversion ratios to oral morphine are variable (between 1:4 and 1:10) tramadol:oral morphine (Wilder-Smith 1994, Grond 1999)
Possible withdrawal reactions on stopping tramadol suddenly

Comparative analgesia/advantages

Less effective than morphine in severe cancer pain but as effective as morphine in moderate cancer pain (Wilder-Smith 1994, Osipova 1991, Rodrigues 1989, Bono 1997)

Less constipation, neuropsychological symptoms and pruritis (in non-blind retrospective study) (Grond 1999)

No studies in neuropathic pain due to cancer, but benefit over placebo in painful neuropathy of other causes. No comparisons with adjuvants or morphine. (Harati 1998, Sindrup 1998)

Pethidine (meperidine)

IM absorption variable, incomplete and erratic.
Inter- and intra-individual variance in blood levels 2-5x.
PO extensive first pass metabolism but in hepatic disease oral availability increases to 80-90%.

Peak plasma concentration at 15-60 min (im) or 120 min (po).
Analgesia may begin<15 min po, <10 min im.

Matablosim by two different pathways:
Hepatic (carboxylesterase) to meperidinic acid (inactive)
Hepatic via cyt p450 to normeperidine (active)

Normeperidine has half analgesic potential of meperidine but 2-3 times potency as CNS excitatory agent

➔ Anxiety, hyperreflexia, myoclonus, seizures and mood changes WITHIN 24 HOURS.

Normeperidine metabolised to normeperidinic acid or hydroxynormeperidine, then renal elimination.

Excretion half life is 2.5-4 hours, 4-5 hours if dose>100mg, >10 hours in cirrhosis. No change in elderly patients.
Excretion half-life of normeperidine is 14-21 hours, increased to >34 hours if renal impairment, elderly.

Elimination half-life of normeperidine is 14-21 or 24-48 hours. Therefore can expect a significant accumulation within 2 days, and steady state at 3-6 days.

Renal dysfunction leads to accumulation of normeperidine.

Dosage

Meperidine 75-100mg im = morphine 10 mg im.
NB Doses of less than 50mg are ineffective.

Toxicity

Repeated large doses over short duration cause CNS toxicity and seizures. Seizures occur after daily doses of 400-600mg. Patients with cancer and renal insufficiency are more at risk of this toxicity.

Analgesia No evidence of better analgesic effect compared with other opioids. May be less effective. Inferior to nonopioids in migraine and generalised post-op pain.

Muscle spasm Equianalgesic doses of meperidine and other opioids cause similar effects on sphincter of Oddi.

Respiratory effects More potent respiratory depressant then morphine.

CNS effects Non-opioid effects, thought to inhibit 5-HT and NA re-uptake. Also anticholinergic SEs. Seizures (do **not** treat with naloxone). Mood changes.

Serotonin Syndrome: Combination of behavioural/cognitive, autonomic and neuromuscular effects. Addiction: More dizziness, impairment of ability to work and greater degree of elation than morphine. Does not produce mydriasis.

Yorkshire Palliative Medicine Guidelines Group
Summary of guidelines on strong opioid use

Use morphine as first line strong opioid orally and diamorphine as parenteral form.

Clinical indication	Opioid
Renal failure	Buprenorphine patch } if pain stable Fentanyl patch } Alfentanil } if parenteral opioid needed Hydromorphone } metabolites may be less toxic Oxycodone } Methadone } use limited by complex pharmacology
Intractable constipation	Fentanyl patch } if pain stable
Intractable nausea and vomiting	Oxycodone
Opioid related itch	Hydromorphone Oxycodone
Confusion	Hydromorphone Oxycodone
Daytime drowsiness	Fentanyl patch
Compliance problems	Buprenorphine patch } if pain stable Fentanyl patch } MXL
Swallowing problems or reduced oral absorption	Buprenorphine patch } if pain stable Fentanyl patch }
Incident pain/painful procedures	OTFC } if good performance status Sc alfentanil SL Fentanyl/sufenatnil
Difficult to control pain with neuropathic element	Methadone

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