

# Opioid use in palliative care



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**The confident and safe use of opioids in palliative care is an essential skill required by all doctors.**

Prejudice, fear and lack of core knowledge contribute to present-day poor opioid administration by doctors caring for patients with intolerable symptoms and pain at the end of life. The core knowledge required for using opioids is relatively simple, but myths and misconceptions regarding morphine still abound in both medical and patient communities. In this article an attempt is made to overcome some of these barriers to good symptom management.

**INDICATIONS FOR OPIOIDS IN PALLIATIVE CARE**

Opioids are primarily used to relieve symptoms of pain and dyspnoea and frequently will also reduce distressing cough and diarrhoea. Their use for the alleviation of terminal restlessness and the induction of sedation is unacceptable. Such practices only perpetuate and reinforce inaccurate beliefs and prejudice regarding opioid analgesics. This may ultimately result in their under-utilisation with subsequent poor terminal symptom control.

**CHOICE OF OPIOID**

Opioids are divided into those with strong and those with weak agonist effects on opiate receptors. I will discuss only the opioids available in South Africa (Table I).

**The core knowledge required for using opioids is relatively simple, but myths and misconceptions regarding morphine still abound in both medical and patient communities.**

Morphine is the opioid drug of choice; it is versatile, affordable and readily available. It is administered orally and has a half-life of about 2 - 2.5 hours. Except in patients in renal failure, it has no danger of accumulation.

With regard to the choice of opioids in palliative care, the pertinent characteris-

*Table I. Opioid choices*

<b>Strong</b>	<b>Weak</b>
<ul style="list-style-type: none"> <li>• Morphine</li> <li>• Fentanyl (Duragesic)</li> <li>• Methadone (Physeptone)</li> <li>• Pethidine</li> <li>• Buprenorphine (Temgesic)</li> <li>• Tilidine (Valoron)</li> <li>• Dipipanone</li> <li>• Pentazocine (Ospronim, Sosenol)</li> </ul>	<ul style="list-style-type: none"> <li>• Tramadol (Tramal, TramaHexal)</li> <li>• Codeine</li> <li>• Propoxyphene (Doloxene)</li> </ul>

## MAIN TOPIC

tics of each drug are highlighted below.

**Transdermal fentanyl** causes less constipation and dysphoria than morphine and accumulates less in uraemic patients. However, it is prohibitively expensive for regular use.

**Methadone** is not available in South Africa in high enough concentrations for regular oral use. It does have unique characteristics, making it useful in some morphine-intolerant patients (very uncommon). Also, it may be more useful in neuropathic-mediated or inflammatory pain syndromes. It has variable pharmacokinetics (half-life up to 10 times longer than that of morphine), making it particularly difficult to titrate for chronic use.

**Pethidine** is not indicated for regular prolonged use in pain control as its metabolite, norpethidine, accumulates quickly, causing central nervous system side-effects such as tremors, multifocal myoclonus and even seizures.

**Buprenorphine** displaces morphine from opioid receptors and may potentiate opioid withdrawal symptoms if given in addition to morphine. It has a half-life of 8 hours and may be administered sublingually. A higher incidence of side-effects, such as nausea and confusion, is often encountered.

**Dipipanone** is only available combined with cyclizine (Wellconal), leading to excessive anticholinergic and sedation side-effects with dose increase.

**Pentazocine** has a higher incidence of side-effects, including thought disturbances and hallucinations if compared with regular morphine.

**Tramadol** is as potent as pethidine parenterally, but orally only as

effective as codeine.

**Codeine** causes more constipation than morphine at equal analgesic doses.

**Propoxyphene** is less potent than codeine; however, it is more effective if used regularly.

### MORPHINE

No other strong opioid shows any clear advantage over morphine. Morphine is versatile and can be prescribed orally in solution (mist morphine), or in tablet form (slow-release formulations). Morphine is also well tolerated parenterally (intramuscular, subcutaneously, intravenously, and intrathecally).

General strategies for initiating doses, increasing doses and changing formulations will be discussed below, as well as the management of common opioid side-effects. The guidelines for complex pain syndromes or the management of opioid-insensitive pain are not discussed here. Guidance in these situations may best be obtained in other literature or by consultation with pain specialists or skilled palliative physicians.

#### Starting morphine

It is usual to start morphine orally and best to use the mist morphine formulation as it has a shorter half-life (2 - 2.5 h) compared with other slow-release formulations. This facilitates faster assessment of pain response to dosing, giving a steady state faster than formulations with longer half-lives. Mist morphine is bitter and may be flavoured with fruit juice or milk.

The starting dose varies according to the age of the patient, the severity of pain and the availability of the patient for ongoing clinical review.

Start the elderly and frail with 2.5 mg and other patients with 5 mg.

The dosing interval should be every 4 hours (to maintain steady-state drug levels). 'As required' or longer dose intervals will result in poor pain control and possibly even in an increase in side-effects.

The 4-hourly dosing interval does not necessarily mean that patients must be woken every 4 hours during the night. This is overcome by *doubling* the last 'retiring' dose, which facilitates better patient sleep and a longer steady state of drug level until the morning, when the patient awakes and 4-hourly dosing is resumed.

The following is an example of the first prescription: mist morphine 10 mg/5 ml; dose: 2.5 ml q4h, 5 ml *nocte* on retiring.

Dose morphine by the mouth and by the clock, attending to side-effects from the first dose.

#### Increasing the dose of morphine

Doses need to be reviewed regularly and increased as dictated by pain. Side-effects do recur at times of dose increase and need to be planned for and actively managed. Doses of morphine every 4 hours are increased by 50% above the previous prescribed dose if pain is not adequately controlled, e.g. 5 mg becomes 7.5 mg and 100 mg becomes 150 mg.

Lower dose increments will be ineffective in managing increasing pain. In exceptional cases morphine doses may be increased over time to greater than 500 mg 4-hourly, as long as side-effects are attended to.

The following is an example of a change in prescription when increasing the dose (50%) and limiting regular dose volumes: Mist morphine 10 mg/5 ml; dose 10 ml q4h becomes mist morphine 100 mg/5 ml; dose 1.5 ml q4h.

**Essential pharmacology**

Morphine is well absorbed from the gastrointestinal tract and metabolised in the liver to morphine-6-glucuronide. The metabolite morphine-6-glucuronide is more potent as an analgesic than morphine, and also reaches higher blood levels an hour after oral ingestion than morphine. The metabolites are excreted primarily by the kidneys and may accumulate in patients with renal impairment. Opioid toxicity is seen in renal impairment but not in severe liver failure. Occasionally preterminal coma patients on opioids may become more restless, with myoclonic jerks, as death approaches. The clinician mistaking these symptoms for pain may increase the morphine dose (not recognising the early signs of opiate toxicity aggravated by accumulation of morphine metabolites because of prerenal failure) and may therefore aggravate the situation.

**Side-effects of opiates/morphine**

The side-effects of opiates/morphine are listed in Table II.

**Constipation** is nearly always encountered and needs aggressive management from the first dose of opioid prescribed. Cancer patients tolerate bulking agents poorly, as they struggle to maintain adequate intake of fluids to stimulate bowel motility. The best option is a combination of a stool softener and a bowel stimulant, e.g. liquid paraffin or sorbitol with senna.

The hand that writes the prescription for opioids must write the script for the aperients.

**Nausea and vomiting** will be encountered in at least 30% of patients, but usually decrease in most patients within a few days. Recurrence of nausea must be

*Table II. Side-effects of opiates/morphine*

Commonly experienced	Less commonly experienced
<ul style="list-style-type: none"> <li>• Constipation</li> <li>• Nausea and vomiting</li> <li>• Sedation</li> <li>• Confusion</li> </ul>	<ul style="list-style-type: none"> <li>• Dry mouth</li> <li>• Sweating</li> <li>• Myoclonus</li> <li>• Biliary colic</li> <li>• Convulsions</li> <li>• Itching</li> <li>• Histamine release</li> <li>• Respiratory depression</li> <li>• Pulmonary oedema</li> </ul>

expected if the morphine dose is increased. The mechanism of nausea is produced predominantly centrally via dopamine effects in the chemoreceptor trigger zone in the floor of the 4th ventricle and occasionally peripherally by delaying gastric motility. The dopamine antagonist haloperidol 1.5 mg daily or metoclopramide 10 mg three times daily is usually adequate to overcome this troublesome side-effect.

**Nausea and vomiting will be encountered in at least 30% of patients, but usually decrease in most patients within a few days.**

**Sedation** is commonly experienced. It is usually mild (dropping off in a light doze if unstimulated). Often patients have had depleted sleep because of uncontrolled pain and may need more sleep to ‘catch up’ after the opioid has controlled the pain. Patients must be reassured that the drowsiness will decrease after a number of days. It may return, to fade again, at times of dose increase. Sedation has many causes and may include

other drug interactions or a change in disease process.

**Confusion** may be caused or aggravated by opiates. It is usually dose dependent, but one must look for other reversible factors or possibly even change the opioid.

**Respiratory depression** is rare if the dose is increased according to the protocols discussed above. One must be alert to opioid-insensitive pain — ‘increasing drowsiness with no improvement in pain control’. Opioids are used successfully and safely to relieve dyspnoea and cough in respiratory distress!

**Useful tips with morphine**

**Breakthrough pain** is rarely constant and at times extra morphine may be required for short periods. It is usual to recommend that the patient takes an extra dose (1/2 usual 4-hourly dose) in these situations. If the regular dose is 20 mg 4-hourly, an extra dose of 10 mg may be taken at any time if the pain is not adequately controlled. This may be repeated at any time during the day. If the patient is using regular breakthrough doses, increasing the regular maintenance dose should be considered.

**Calculate 24-hour opioid consumption.** This is helpful if one needs to:

- change the type of opioid used (charts are available to convert to a different opioid for equal anal-

## MAIN TOPIC

- gesic potency)
- change to using a syringe driver (24 hour subcutaneous infusion of medication) (discussed below)
  - change mist morphine (oral) to slow-release morphine (oral).

Parenteral doses of morphine are twice as potent as oral doses.

The regular dose of mist morphine 30 mg every 4 hours (oral) equates to a 24-hour dose of 180 mg of morphine (oral). Therefore one would add 90 mg of morphine sulphate to the syringe driver over 24 hours (6 ampoules of 15 mg/ml) for a subcutaneous infusion.

**Use morphine to suppress cough and dyspnoea** at doses lower than those required for treatment of pain.

**Re-evaluate doses regularly** .

**Psychological addiction** to morphine does not occur if it is prescribed for pain relief.

**Physical dependence** does occur, and if for some reason the need for opioids decreases then the dependence is always managed successfully by a 25% daily dose decrease every 3 - 4 days.

**Patient education.** The success of opioid prescribing and pain control is directly related to how well doctors educate patients and prepare them for the side-effects, and how successfully the latter can be controlled. Many brochures are available free of charge.

### ORAL MORPHINE – INFORMATION FOR PATIENTS AND FAMILIES

Morphine is obtained from the juice of the opium poppy and acts on pain centres in the brain and spinal cord. Millions of people have used morphine for pain after surgical operations and for pain caused by cancer. Some patients need to take it for years and others for only a few days.

It is used to relieve pain, so improving one's quality of life. There is no upper limit to the dose of morphine that one may take. The dose of morphine may also safely be decreased if one's pain declines in intensity. Many people fear addiction to morphine. One does not become addicted to morphine, but one does need to decrease its administration slowly under supervision if it is no longer necessary. This occurs without any adverse effects.

Your doctor will supervise your dose of morphine. Your pain is usually ongoing and therefore you would need to take morphine regularly by the clock.

Morphine does have side-effects including constipation, nausea and vomiting and some drowsiness. In most cases these side-effects are easily overcome and successfully managed. They also tend to decrease after a few days of taking morphine. Discuss these effects with your doctor. You would need to take medicine regularly to overcome the constipation.

One's pain is rarely constant and may increase for short periods. Your doctor will decide how much extra morphine you may take during this period.

If you feel that the morphine or your pain is not under control, please feel confident to discuss it with your doctor or specialist. Others who may be able to help may include hospice-trained staff (nursing or medical), pain specialists or cancer nursing organisations. Help is only a call away.

### FURTHER READING

- Back I. Opioid analgesia. *Topics in Palliative Care 1997 – Study Aid.*  
Pack I. Pain. *Topics in Palliative Care 1997 – Study Aid.*  
Doyle D, Hanks GWC, MacDonald N. Opioid analgesic therapy. In: *Oxford Book of Palliative Medicine.* Butler and Tanner. 1999.  
Twycross R, Lack S. *Oral Morphine Information for Patients, Families and Friends.* Beaconfield Publishers. 1991.

### IN A NUTSHELL

The confident use of morphine in palliative care requires core knowledge of its pharmacology and a confident understanding of the strategies to increase the dose.

Dose by the mouth and by the clock.

The hand that writes the script must attend to constipation and have a strategy for nausea control.

If pain is not controlled or improved by 2 - 3 dose increases it is probably a partially opioid-insensitive pain. Consider the use of co-analgesics.

Good patient preparation and proper opioid use can only remove present prejudice and fear for patients and doctors alike.