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Focus

Recommendations for pain management in palliative care

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GENERAL POINTS

- Consideration should always be given to diagnosing and treating the underlying cause of pain with the use of measures such as surgery, chemotherapy, radiotherapy and other treatment modalities (including nerve blocks, physiotherapy, non-analgesic drugs and psychotherapy).
- There may often be a psychological component to the pain which can be aided by team members spending time to help reduce anxiety, anger or other emotional reactions. Therapeutic aspects of the consultation, such as explanation of symptoms and support, may be valuable in lessening pain.
- Analgesics often need to be given regularly (sometimes for months or even years) rather than on an as required basis, to prevent pain recurring. Regular dose review is indicated as the needs for analgesia change, eg, from disease progression.
- Oral administration of drugs is preferred where possible.
- Some patients may obtain pain relief from adjuvant drugs (eg, antidepressants, anticonvulsants, corticosteroids), used in conjunction with (or on occasion instead of) conventional analgesics (see Table 1).

ANALGESIC LADDER

A step-wise approach of analgesic drugs in the management of pain, moving from non-opioids through weak opioids to strong opioids, is recommended. This is in accordance with the validated WHO (World Health Organization) analgesic ladder.[3,4]

Paracetamol is usually the first agent used. Weak opioids such as codeine, dihydrocodeine or tramadol are the second step, followed by stronger opioids. However, in practice some palliative care specialists admit that they bypass the weak opioid option and move directly to morphine use.

There is evidence that combining optimal doses of non-opioids with weak opioids produces an additive analgesic effect greater than that obtained by doubling the dose of either constituent administered

KEY POINTS

- Analgesia for chronic pain should be given regularly to prevent pain recurring
- A step-wise approach of analgesic drugs, moving from non-opioids through weak opioids to strong opioids, is recommended
- Morphine doses should be titrated using immediate release formulations and maintained with controlled release products
- The oral route is optimal for morphine administration
- Subcutaneous continuous infusion is preferred when parenteral administration is required
- Adjuvant analgesic regimens can be individually tailored

The study details for these

alone, and that the adverse effects produced by such combinations are less than would be produced by an equi-analgesic dose of a single constituent.[5]

recommendations may be found in the Original Research section, page 53.

TABLE 1. ADJUVANT ANALGESIC DRUGS
Adjuvant analgesics (co-analgesics) can be used in conjunction with normal analgesics. This is a basic list

Drug type	Examples	Indication
NSAID	Voltaren Naproxopen Ibuprofen Celecoxib	Bone and inflammatory pain
Tricyclic antidepressant	Dothiepin Amitriptyline Trimipramine Nortriptyline	Neuropathic pain. Low dose (sometimes full antidepressant dose required)[1]
Anticonvulsant	Clonazepam Carbamazepine Sodium valproate Gabapentin[a]	Neuropathic pain. Low dose
Corticosteroid	Prednisone Dexamethasone Methyl prednisolone Betamethasone	Headache related to raised intracranial pressure; inflammatory pain; capsular pain (eg, hepatic); pain due to oedema secondary to obstruction of hollow viscus

[a] While gabapentin is increasingly used for neuropathic pain, evidence suggests that it is not superior to carbamazepine[2]

Adjuvant drugs can be added at any stage. The choice of co-analgesic will depend on the type of pain that is being treated.[6] See Table 2 for examples of analgesics.

The key to successful pain management in palliative care is to carefully tailor the treatment to control the pain:

- accurately determine the cause and nature of the pain
- choose the appropriate analgesic and adjuvant agents, and other non-medication pain relief measures
- frequently reassess pain control and make necessary adjustments.
- Reassessment may need to be daily at some stages for initiating/adjusting therapy. This may involve house calls or home visits, telephone calls, or using the services of a nurse. Occasionally, shortterm admission might be helpful to stabilise and monitor pain control.

PAIN ASSESSMENT

Not all terminally ill patients require analgesia. Between 15 and 30 per cent of cancer patients have no pain.[8,9] Of those who do, there are three common pain varieties: visceral, bone and nerve pain.

Visceral pain
This is usually dull and poorly localised, and is likely to be opioid-responsive.

Bone pain
This will be well-localised, locally tender, and dull in nature. Its cause can often be confirmed by x-ray or bone scan. Radiotherapy usually helps. This pain is NSAID-responsive and partly opioid-responsive. Paracetamol may be of value on occasion.

Nerve pain
This may be burning, aching, tingling or shooting in nature and be associated with sensory changes. It is partly opioid-responsive but almost always requires co-analgesics such as low-dose amitriptyline; clonazepam, or sodium valproate. Steroids may be worth trying for possible functional neuropathic pain (eg, reversible peri- tumour oedema compressing pelvic nerves).

USE OF MORPHINE

Morphine is still the "gold standard" for analgesia. When used properly, oral morphine has been shown to effectively relieve chronic cancer pain in 75 to 90 per cent of patients.[10]

The dose of morphine is titrated-up to achieve adequate pain relief. There is no upper limit of

dose, but most patients will not need daily doses above 200-300mg orally. If patients require more, and are not getting good analgesia, seeking a pain or palliative specialist's opinion is recommended, depending on the individual GP's experience and training.

Oral administration
Ideally, two types of formulation are required:

- immediate release (for dose titration). Formulations available in New Zealand are morphine hydrochloride (RA-Morph) and morphine sulphate (Sevredol).
- sustained release (for maintenance treatment). Formulations available in New Zealand are Kapanol, MST continus and LA Morph (all morphine sulphate).

Dose titration of oral morphine
Starting dose: start at 2.5 to 10mg. A dose of immediate release morphine is given every four hours and the same dose is used for breakthrough pain. This rescue dose may be given as often as required (eg, every hour). The total daily dose of morphine can be reviewed daily. In the elderly and opiate-sensitive, low doses might be adequate. Half-strength rescue doses (rather than full/same strength) might be sufficient, especially in cases where there is concern about toxicity or when the dose is high. The starting dose also depends on liver and renal function and prior analgesic requirement (eg, 5mg morphine may be inadequate if moving up from tramadol).

Regular dose: the regular (sustained release) dose can then be adjusted according to the total daily dose of morphine. The total dose of immediate release morphine given over a period of 24 hours is calculated. This dose is then administered in the form of a sustained release preparation over 24 hours. If pain returns consistently before the next regular dose is due, consideration should be given to increasing the regular dose.

Other considerations: in general, immediate release morphine does not need to be given more often than every four hours after the titration period, and sustained release morphine no more often than every 12 hours.

In some specialists' opinion, there is a place for the occasional administration of MST eight-hourly rather than 12-hourly, if breakthrough occurs six to eight hours after the 12-hourly dose.[11] However, Kapanol should not be given more frequently than 12-hourly, and frequently 24-hourly is sufficient.

Once a maintenance treatment has been established using sustained release morphine, the patient should also be prescribed immediate release morphine to use for breakthrough pain. This dose is usually 15 to 20 per cent of the total daily dose of morphine.

For many patients receiving immediate release morphine every four hours, a double dose at bedtime is a simple and effective way of avoiding being woken by pain. Sedative use is an alternative to this.

Rectal or subcutaneous administration
If patients are unable to take drugs orally, alternative routes for morphine are subcutaneous, rectal or transdermal. The preferred alternative route from oral is usually subcutaneous. [12]

The dose and the duration of analgesia of morphine is said to be the same for rectal and oral routes[13] (see Table 3), although the state of the rectum and the positioning of the suppository in the rectum may affect mucosal absorption. It is currently

TABLE 2. ANALGESIC MANAGEMENT OF CHRONIC PAIN

Degree of pain	Type of analgesic	Examples	
Mild	Non-opioid	Paracetamol	1000mg q6h to q4h
Moderate	Weak opioid	Dextropropoxyphene	100mg q4h
		Codeine[a]	60mg q4h
		Dihydrocodeine	60 to 120mg q12h
		Tramadol[b,c]	50 to 200mg q6h
Severe	Opioid	Morphine	5 to 10mg q4h (starting dose)
		Fentanyl[b]	25 µg/hr, 2.5mg/q72h [transdermal] (starting dose)
		Methadone[d]	2.5 to 5mg q12h (starting dose)

[a] Effect relies on metabolism to morphine, hence of no benefit to a minority of the population who lack metabolising enzyme.
[b] Prohibitive cost and lack of subsidy in New Zealand restricts use.

[3] Reduced opioid side effects (constipation, depressed respiration, sedation).[7]
[4] Should only be started by, or in consultation with, an experienced prescriber.

recommended that the same dose and dose interval be used when changing from oral to rectal administration, although some dose adjustment may be needed subsequently.[14]

Morphine suppositories are available for rectal use. The formulation available in New Zealand is RMS suppositories (morphine sulphate). Controlled release morphine tablets should not be crushed or used for rectal or vaginal administration. Rectal MST has been reported to work well if no alternatives are available.

The dose for subcutaneous use is a third to a half that for oral (see Table 3).[16] There is generally no indication for giving morphine intramuscularly for cancer-related pain because subcutaneous administration is generally simpler. On rare occasions an IM injection might be preferable (eg, if the patient is shocked or has poor subcutaneous circulation and IV is not an option). Morphine may be given subcutaneously by continuous infusion, or initially as bolus injections every four hours until an infusion pump (syringe driver) is available.

Intravenous administration

Intravenous administration is indicated in patients where the subcutaneous route is not practical – eg, in patients:

- with generalised oedema
- who develop erythema, soreness, or sterile abscesses with subcutaneous administration
- with coagulation disorders
- with very poor peripheral circulation
- who are shocked.

Intravenous administration may also be the best parenteral route in patients who, for other reasons, have an indwelling central or peripheral line. However, subcutaneous infusions may still be preferable even when IV access is available, to minimise the peak dose effects of IV morphine boluses.

Continuous infusion can be administered via a syringe driver.

The dose for intravenous use is said to be a third of an effective oral dose (see Table 3).[17]

Other administration routes

Buccal, sublingual and nebulised routes are generally not recommended because it is considered they have no clinical advantage over conventional routes. The use of nebulised morphine is being explored, but only one out of eight randomised controlled trials to date has found any beneficial effect of nebulised opioids over nebulised normal saline.[18] Sublingual or transdermal use of other opioids may be an alternative to subcutaneous administration (see above).

TABLE 3. MORPHINE RELATIVE POTENCY RATIOS	
Oral to rectal	1 : 1
Oral to subcutaneous	1 : 3 to 1 : 2
Oral to intravenous	1 : 3

ALTERNATIVE OPIOIDS

For moderate to severe pain, or for those who cannot tolerate morphine, use of the opioids fentanyl and methadone can be considered as alternatives to morphine. Other alternative drugs include dextro-moramide (palfium). This is short-acting so had an indication for that reason, but is no longer available in New Zealand. Similarly, hydromorphine and diamorpine are not available in this country.

In patients who have difficulty swallowing, sublingual buprenorphine (Temgesic) has been used in the past as an alternative to low dose oral morphine – however, this is now not generally recommended. It should not be used in a patient already on morphine because it is a partial agonist and will replace morphine at the receptor site. This could result in a paradoxical increase in pain, or symptoms of withdrawal from morphine. If the patient is on buprenorphine and morphine is added, the effect of morphine will be delayed due to receptor occupation by buprenorphine. Fentanyl is available by a transdermal delivery system (Durogesic patch) with a controlled systemic delivery of the drug for 72 hours. Unfortunately it is not currently listed in New Zealand under the tariff, but does offer an effective alternative with some advantages and disadvantages compared with morphine.

SUMMARY

Following these recommendations should produce effective control of cancer pain in the majority of patients. Other methods are required for the remaining few per cent, and referral to a pain or palliative medicine physician is recommended.

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