Pain management in palliative care

An update

Kirsten Auret
MBBS, FRACP, FAChPM, is Senior Lecturer, School of Medicine and Pharmacology, University of Western Australia, and Medical Director, Palliative Care Unit, Hollywood Private Hospital, Perth, Western Australia.
auretk@cyllene.uwa.edu.au

Sarah Pickstock
MBBS, FAChPM, MA, is Staff Specialist, Palliative Care Unit, Hollywood Private Hospital, Perth, Western Australia.

BACKGROUND
Pain is a common and feared problem for those with advanced cancer. The goal of palliative care is to relieve suffering and improve quality of life. A step-by-step approach allows good symptom management and minimisation of drug side effects.

OBJECTIVE
This article aims to improve the general practitioner's confidence in prescribing in the palliative care setting and to encourage early involvement of community palliative care teams.

DISCUSSION
Opioid initiation and substitution, and the role of other medications and nondrug therapies in controlling cancer pain are discussed.

Case history – Jocelyn
Jocelyn, 64 years of age, and mother of three children, was diagnosed with metastatic adenocarcinoma of the lung 9 months ago after investigation for back pain revealed a T9 metastasis and a primary lesion in the right lung. Initial treatment was radiotherapy to the painful bone metastasis with good results and Jocelyn elected not to pursue chemotherapy. She now presents with severe pain in the right groin, which radiates to her knee, and difficulty walking. An X-ray demonstrates lytic lesions in the right acetabulum, pubic rami and intertronchanteric area of the femoral head.

Good pain management is one of the central pillars of good palliative care. Pain is a prevalent and feared symptom – both in patients with cancer and in those dying of nonmalignant diseases such as chronic obstructive airway disease.[1] However, pain can be controlled using easily available medications in more than 80% of patients,[2] therefore much of day-to-day palliative care is not so much about what is 'new' but about prescribing well with what we have had for a while.

Management of malignant bone pain

Jocelyn has malignant bone pain and the treatment of this may require multiple modalities. The mainstay of drug therapy includes regular paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs) and an opioid. The opioid should be prescribed as a background around-the-clock dosing and as 'breakthrough' doses to cover spontaneous and movement induced flares in pain (*Table 1*). There is no strong evidence that one particular NSAID is better, nor that COX-2 inhibitors are any more effective, and so the choice should be made on the basis of side effects. Radiotherapy can be very helpful. A Cochrane review[3] found that single fraction radiotherapy produces significant pain relief in almost 50% of patients at 1 month. Bisphosphonates also have some analgesic action, although the effect is delayed (number needed to treat [NNT] for 50% pain relief at 1 month is 11). It would be most relevant to consider bisphosphonates for patients able to receive treatment through the Pharmaceutical Benefits Scheme (PBS) for long term control of bone events in those with breast cancer, prostate cancer, or myeloma, or those

with hypercalcaemia of malignancy. Consider orthopaedic intervention for those with incipient pathological fracture of long bones – indicated by marked cortical erosion – as results of intervention are good. Complementary therapies may improve psychological wellbeing and possibly make a further impact on pain control.[4]

Why introduce an opioid now?

Patients such as Jocelyn with severe or rapidly escalating cancer pain should commence a potent opioid as these have proven benefit in the control of cancer pain. Codeine has no efficacy or tolerability advantage over an equipotent dose of morphine. The likelihood of escalating pain in the coming period requires prescription of an opioid with no therapeutic ceiling. Well conducted clinical studies have shown that potent opioids have no significant risk of addiction in those with cancer pain.[9] Slow release nonparenteral routes remain the preferred method of providing chronic opioid therapy. Morphine is the usual choice in this situation and is available in oral once or twice daily dosing formulations, immediate release tablets, elixir, and injections. It remains first line therapy as it is well established in cancer pain management, relatively inexpensive, easy to obtain, and is available in doctors' bags as an injectable backup.

What are the new options?

Alternate potent opioids such as oxycodone, hydromorphone and fentanyl are now available in Australia. These may be used at opioid initiation or if inadequate analgesia or unacceptable side effects occur with morphine ('opioid substitution') (*Table 2*). Transdermal fentanyl patches are a suitable alternative to morphine, especially in clinical situations where oral dosing is difficult such as head and neck malignancy, or when vomiting or bowel obstruction is problematic. Methadone is increasingly used for opioid substitution due to postulated efficacy for neuropathic pain and its lack of active metabolites. It has a long and variable half life resulting in difficulty establishing equianalgesic (ie. producing the same level of analgesia) ratios and the risk of drug accumulation.[5] There is also an increasing place for tramadol. Tramadol is a centrally acting analgesic that is structurally different to the opioids and acts as a weak stimulator of opioid receptors while inhibiting noradrenaline and serotonin reuptake.[6] It causes less constipation, and although there have been concerns about the dose ceiling of 400 mg per day, there is increasing use of higher doses in palliative care with little evidence of serotonin syndrome being a significant risk.[7]

For some malignancies, palliation of pain may be with antitumour therapy (eg. chemotherapy or hormone therapy) or radioisotope treatment (eg. samarium/strontium for metastatic cancer of prostate or breast).

Table 1. Initiating morphine

- Reassure the patient about the safety and efficacy of opioids
- Prescribe a laxative and antiemetic
- For opioid naive patients:
  - 2.5–5.0 mg of morphine elixir/immediate release tablet 4 hourly + equal dose to be taken PRN between regular doses if pain is not controlled
  - if pain is not controlled, increase each dose by 25–50%
  - when dosing is stable with good pain control, convert daily dose to a once or twice daily slow release preparation
- review daily during the titration phase (this can be done by phone)

Calculating breakthrough doses

- Traditionally 1/6 of the total daily opioid requirement has been used for PRN dosing. This does give an idea of the starting dose, which can be adjusted according to effect. Some patients will need smaller doses, some larger

Table 2. Approximate equianalgesic potencies of opioids in chronic dosing

Opioid	Dose equivalent to 30 mg morphine (PO)	Ratio (morphine PO: new analgesic)
Morphine (SC, IM, IV)	10 mg	3:1
Oxycodone (PO)	20 mg	1.5:1
Hydromorphone (PO)	6 mg	5:1
Hydromorphone (SC, IM, IV)	3 mg	10:1
Methadone (PO)	5 mg	6:1 (conversion ratio increases with higher doses of morphine, seek specialist advice)
Tramadol (PO, SC, IM, IV)	300 mg	1:10
Codeine (PO)	360 mg	1:12
Fentanyl patch (topical)	More complex – see conversion table in product disclosure (available on E-MIMS)	

There is no definite role for the buprenorphine ('Norspan') patch, which is a mixed opioid agonist/antagonist. Pethidine should not be used, as it can accumulate with repeated dosing – especially with renal impairment or dehydration – and cause neurotoxicity.

For 'breakthrough' pain, the ideal drug would be of rapid onset and short duration of action. Fentanyl lozenges ('Actiq') are a transmucosal preparation specifically designed for this indication. However, its use is currently limited as it is not PBS listed. Immediate release morphine is frequently used, but is complicated by slow onset of action and duration of action of several hours. Immediate release oxycodone or hydromorphone are alternatives but have the same problems.

What about opioid adverse effects?

The biggest long term adverse effect will be constipation, less so with fentanyl and tramadol. Always prescribe aperients (eg. 'Coloxyl and senna', 'Movicol'). Other adverse

effects such as nausea and sedation occur in the majority of patients. Tolerance develops to these side effects in most patients within a week. Metoclopramide or an alternative antiemetic should be given to use as required at the same time as the first prescription of opioid or tramadol. Ongoing nausea may be tumour related rather than due to the opioid. Long term sedation occurs in less than 10% of patients,[8] however patients should be advised to avoid driving at initiation of opioids and with any significant increase in dosage.[9] Others adverse effects such as itch, sweating, urinary retention, anaphylaxis, and opioid induced neurotoxicity are uncommon, and can be managed through dose reduction or opioid substitution.[5,10] There is no evidence that appropriate prescription of opioids shortens prognosis.

Case history – Jocelyn, continued

Jocelyn's symptoms have been successfully managed with paracetamol 1 g four times per day, naprosyn 500 mg twice per day, and 'MS Contin' 70 mg twice per day, along with monthly intravenous zolendonate (commenced because of hypercalcaemia), a single fraction of radiotherapy to the pelvis, and hypnotherapy. Her orthopaedic surgeon elected to take a 'wait and see' approach as the femoral cortex was still thick, despite the metastasis.

Several weeks later Jocelyn represents with two new pains – increasing dull ache in the right anterior chest, and a severe pain in the mid back radiating bilaterally to the area around the umbilicus, and associated with a painful sensation on light touch and pins and needles.

Management of visceral pain

Jocelyn's chest pain is from the enlarging primary cancer within the lung and should respond to increased doses of opioids. Paracetamol is useful to add if the patient is not already taking it. Dexamethasone may reduce peri-tumour oedema in an encapsulated organ and therefore may reduce visceral pain. Co-prescription of steroids plus NSAIDs may increase the risk of gastrointestinal symptoms. Consideration should be given to also prescribing a proton pump inhibitor.

Management of neuropathic pain

The latter pain Jocelyn describes is neuropathic. Awareness of it is very important as it will be less opioid sensitive than pain of nociceptive origin and adjuvant medications will be required (*Table 3*). Adjuvants are not traditional analgesics but play a role in suppressing abnormal activity in damaged nerves or reducing central sensitisation. Anticonvulsants and tricyclic antidepressants are the mainstays of therapy, with their efficacy in palliative care extrapolated from studies on diabetic neuropathy and postherpetic neuralgia. Gabapentin and pregabalin are the newer options. Number needed to treat or number needed to harm (NNH) data is available through several reviews on neuropathic pain management available in the Cochrane Library. The symptoms Jocelyn has may relate to a spinal cord compression – magnetic resonance imaging (MRI) is the imaging of choice. This will require consultation with your local palliative care specialist, emergency department or oncologist. If confirmed, acute treatment is with high dose dexamethasone (16 mg intravenously or subcutaneously) and referral for radiotherapy, neurosurgery and/or orthopaedic intervention.

Table 3. Neuropathic pain symptoms and signs

- Radicular/dermatomal distribution
- Quality of pain: burning, tingling, pins and needles, electric shock-like, pain in a numb area, phantom pain
- Associated features: numbness, weakness, abnormal reflexes
- Allodynia: pain caused by light touch
- Hyperalgaesia: extreme sensitivity to potentially painful stimuli
- 'Wind up': rapidly escalating pain with decreasing opioid responsiveness

What about when the pain seems intractable?

Most often, poor pain control is due to a combination of clinician factors (eg. opioid phobia, focus on 'disease' not symptoms, lack of awareness of guidelines and resources) or patient concerns (eg. fear of addiction, tolerance and side effects, stoicism).[11] Earlier intervention is more likely to control pain in the longer term. Intractable pain requires specialist advice – review pathology (eg. is a pathological fracture, cord compression, hypercalcaemia, or existential distress being missed?); is it neuropathic pain; is 'wind up' occurring? Options include ketamine (eg. by 5 day subcutaneous infusion 'burst' protocol),[12] spinal analgesia, or terminal sedation if the patient is at the end of their life. Admission to monitor effect and re-titrate the opioid dose will be required if ketamine is used.

Summary of important points

- Cancer pain can be well controlled in most patients.
- Opioids are safe if titrated to effect.
- Pethidine is not a good drug for chronic cancer pain management.
- Pain must be considered along with other symptoms

such as nausea, anxiety or depression.
- Patients need both regular and as required medications for pain.
- Families need information and support.
- Consider early referral to community palliative care services.

Resources
- Therapeutic guidelines: Palliative care. version 2 (e-version and palm pilot versions available)
- Palliative care drugs. Available on PBS website at www9.health.gov.au/pbs/scripts/listther.cfm?sched=PA
- Cochrane Library at www.Cochrane.org

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afp **CORRESPONDENCE** email: afp@racgp.org.au