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REVIEW

Inpatient pain management of cancer patients

RE Hodgson

Department of of Anaesthesia, Critical Care and Pain Management, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, South Africa
Corresponding author, email: *eric_hodgson@mweb.co.za*

Pain is a major concern in up to 70% of cancer patients. Pain may be the presenting feature, as an exacerbation during medical or surgical therapy or at the end-of-life during palliative care.[1]

It is important to recognise that medications only form part of a multidisciplinary approach to the bio-psycho-social approach to pain management in all forms of pain, including cancer pain.

Particularly in South Africa, where so many races and cultures are represented, these differences are often not considered in the management of cancer pain.

Principles of the management of cancer pain should include:[1]

1. **Patient and family centred care** – may be difficult in South Africa due to the differences in both patient and staff socio-cultural backgrounds and widely disrupted family connections. However, such connections should be recognised and facilitated when creating these guidelines, group, and individual needs.
2. **Individualised for each patient** – while there are protocols for chemotherapy and certain aspects of care for the cancer patient, there is a definite need for individualised care, particularly in pain management.
3. **Interdisciplinary team** – the oncologist is the team leader. This team could include, but is not limited to, an anaesthesiologist/pain specialist, psychiatrist, psychologist, pain specialist nurse, physio- and occupational therapist.
4. **Pharmacological therapy** – drugs are one of the components of the bio-psycho-social approach to chronic non-cancer pain that can be applied equally to cancer pain. Given the severity and often short duration of cancer and thus pain, there is an increased focus on cancer pain.[2]

Multimodal analgesia

The value of using multimodal analgesia is widely accepted with the purpose of improving analgesia with drugs having different modes of action.

Opioids are the most effective analgesics but also have the most immediate severe side effects of respiratory depression, that may be fatal.

Minimising the dosages will decrease side effects of each drug while maintaining efficacy.[3]

The components of a multimodal analgesic regime include:[4]

1. Baseline anti-hyperalgesic drugs[4]
   a. Paracetamol
   b. Nonsteroidal anti-inflammatory drugs (NSAIDs), especially the COX-2 inhibitors
      i. COX-1 inhibitor – Ketorolac
      ii. COX-2 inhibitor – Parecoxib
2. Adjuvant drugs[5]
   a. Adjuvant drugs
      i. Antidepressants – tricyclic
      ii. Anticonvulsants – gabapentin/pregabalin
      iii. Specific tumours
   b. IV/subcutaneous:[4]
      Morphine ± ketamine ± dexmedetomidine ± magnesium ± lignocaine
   c. Transition to oral
      i. Morphine/oxycodone
   d. Transdermal – fentanyl/tramadol

Paracetamol[4]

It is widely accepted that paracetamol is an effective baseline drug in pain management strategies. The introduction of intravenous paracetamol has facilitated the incorporation of the drug into oral cancer where oral/rectal administration may not be possible or desirable. Intravenous administration of paracetamol bypasses the liver with two main beneficial effects:

- Hepatic exposure to paracetamol is reduced as paracetamol is delivered via the hepatic artery (20–30% of liver blood flow/dose) rather than the portal vein (70–80% of hepatic blood flow/100% of oral/rectal dose).
- Plasma levels of IV paracetamol are 20–30% higher than equivalent oral/rectal doses, which appear to be associated with improved efficacy in clinical use and are thus useful as initial therapy in hospital.

Paracetamol can be transitioned to oral therapy at a dose of 1 g 6 hourly.

Concerns have been raised about the detrimental effects of paracetamol on hepatic function, particularly in the elderly (> 65), with the FDA recommending that the maximum dose of

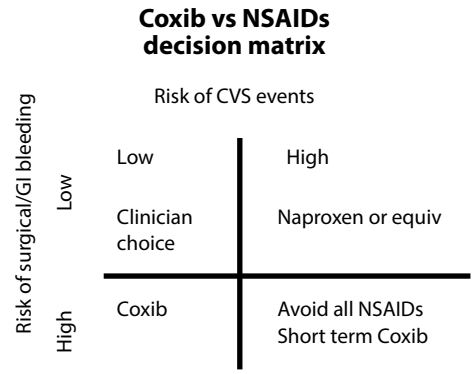

Figure 1: Decision matrix to guide NSAID prescription in the postoperative period

paracetamol in over the counter (OTC) preparations be reduced from 500 mg to 320 mg.

A single dose should not exceed 20 mg/kg (15 mg/kg in those ≥ 65) and the total daily dose should not exceed 4 g (3.5 g in those ≥ 65).[4]

Nonsteroidal anti-inflammatory drugs

NSAIDs are effective in cancer pain that is particularly effective in hyperalgesia associated with movement.[4]

Adverse effects and contraindications may limit the use of NSAIDs in cancer pain.

Adverse effects differ depending on the class of drugs used.

The non-selective or class 1 NSAIDs (including ibuprofen, diclofenac, and ketorolac) interfere with platelet function (with resultant wound bleeding) and can cause peptic ulceration, bronchospasm and allergy.

Coxibs, which are specific inhibitors of cyclo-oxygenase 2 (COX-2), have no anti-platelet activity and reduced effects on the gastric mucosa.

The choice of NSAID for the management of postoperative cancer pain can be facilitated by the application of the decision matrix (Figure 1).

In appropriately selected patients, NSAIDS improve pain relief by limiting hyperalgesia, especially for dynamic pain, thereby facilitating mobilisation and adequate cough. Other advantages include a reduction in the incidence of nausea, vomiting, ileus and sedation by reducing opioid requirements.

All NSAIDs have the potential to worsen renal function, particularly in patients with pre-existing renal dysfunction and those who are hypovolaemic through reduced oral intake and high opioid administration.

Adjuvant drug dosages[5]

1. Antidepressants
   a. Tricyclic: amitriptyline, nortriptyline
      i. 10–100 mg nocte (25 mg increments)
   b. Serotonin norepinephrine reuptake inhibitors (SNRIs)
      i. Venlafaxine: 75–300 mg mane (75 mg increments)
      ii. Duloxetine: 20–60 mg mane (20 mg increments)
2. Anticonvulsants
   a. Gabapentin: 300 mg TDS/BD (Max 3 600 mg/day)
   b. Pregabalin: 50 mg TDS/BD (Max 300 mg/day)
3. Specific drugs
   a. Bisphosphonates:[6] dosage varies with drug and tumour type
      i. Primary bone tumours
      ii. Secondary tumours: particularly breast and prostate
   b. Corticosteroids:[7] dexamethasone is most used where nerve root or spinal cord compression is symptomatic in palliative care.
      Dose is titrated to clinical effects and side effects.
      Longer term use is limited by side effects, including weight gain, hypertension and exacerbation of chemotherapy induced immunosuppression.
   c. Cannabinoids: various compounds have been described with positive effects on reduced nausea and vomiting and improved appetite.
      However, there have been no randomised control trials demonstrated beneficial effects of cannabinoids.[7]

Compound analgesic drugs

South Africa has the misfortune of having over 30 registered compound analgesics.

These compounds are supposed to improve patient convenience and compliance, but really provide inadequate pain relief due to the dose of opioid being limited by the concurrent paracetamol and/or NSAID being at toxic levels before achievement of adequate opioid dosing.[6]

Several compound analgesics contain completely inappropriate drugs, including:

a. Meprobamate:[7] Stopayne®, Stilpayne®, Synaleve®, etc.: is a carbamate major tranquiliser with no proven efficacy in pain management. Meprobamate is a hepatic enzyme inducer that shortens the effective duration of both codeine and paracetamol. Meprobamate is also highly addictive, resulting in physical and psychological dependence within as few as 10 days.[5]

b. Caffeine:[8] Syndol®, etc. is included in compound analgesics to supposedly reverse opioid-induced sedation. Caffeine has a limited role in analgesia and may contribute to medicine over-use headache by causing caffeine-withdrawal headache and thus initiating a vicious cycle of headache – caffeine containing analgesic – caffeine withdrawal headache – caffeine containing analgesic been a limited number of opioid analgesics available to South African clinicians treating acute pain.

Compound analgesics should have no more than three components: paracetamol ± NSAID ± opioid (adequate dose). Even better is to have a combined paracetamol + NSAID for baseline pain relief and an opioid dosed independently for rescue.

Oral opioids

Codeine

Codeine is very commonly used but has two major disadvantages:

a. Doses of codeine, when used in most compound analgesics in South Africa are inadequate. The recommended adult dose of codeine is 60–120 mg 4–6 hourly. Most compound analgesics provided in South Africa only 30–40 mg of codeine before toxic levels of the co-administered paracetamol and/or NSAID are reached.

b. Metabolism by cytochrome (CYP) to morphine by three enzymatic variants resulting in metabolism as follows:[6]

   1. **Ultra-rapid** – resulting in potentially fatal levels of morphine that may result in death as seen in a child post-tonsillectomy in the USA, leading to a recommendation from the FDA that codeine be withheld from paediatric pain management.[9]
   2. **Normal metabolism** – seen in the majority of persons taking codeine, resulting in morphine analgesia with varying onset and duration.
   3. **Slow metabolism** – patients will characteristically complain of inadequate pain relief with codeine but still experiencing constipation, caused by unmetabolised codeine.

Tramadol

Tramadol also requires CYP metabolism to generate an M1 metabolite that provides opioid analgesia. In addition, tramadol provides pain relief by serotonin and noradrenalin re-uptake inhibition, thereby augmenting descending inhibitory pathways at a spinal cord level.[10]

Serotonin levels may be raised by other drugs such as the SSRI and tricyclic antidepressants raising the risk of serotonin syndrome.

Raised serotonin also causes nausea and vomiting via interaction with the 5HT-3 receptor. Treatment with 5HT-3 antagonists such as ondansetron and granisetron will theoretically reduce tramadol analgesia but this has not been found clinically.

Morphine[11]

While an extremely efficient analgesic, morphine is seldom used outside pain clinics for treatment of non-cancer pain. When oral morphine is used, care should be taken when prescribing for patients with impaired renal function.

Morphine is active at opioid receptors and the majority is excreted as the inactive metabolites, morphine 2 and 3 glucuronides. However a significant amount is excreted via the active metabolite, morphine 6 glucuronide, that accumulates, that causes respiratory depression leading to death.

Morphine is the mainstay of cancer pain treatment.

Oxycodone[12]

Oxycodone has twice the potency of morphine and has an oral bioavailability of 60% as opposed to 30% for morphine. Side effects such as pruritis and nausea are reduced but constipation is still seen.

Oxycodone metabolites are inactive, so side effects are not affected by renal function. Oxycodone dosing is 30–40% of that required for morphine.

Onset of analgesia is seen at 20–30 minutes, similar to morphine.

Where pain could be expected to persist for more than 48 hours, an extended-release (ER) preparation (Oxycontin®) may be used at a dose of 0.2–0.4 mg/kg 12 hourly with immediate-release oxycodone given at 2–4 hourly intervals at a dose of 0.2 mg/kg for breakthrough pain.

Similar to SR morphine, the SR preparation may need to be given 8 rather than 12 hourly.

Opioid requirement for outpatients

Hospital is the ideal opportunity to determine the patient's requirement for opioid pain relief.

For severe pain, adjuvants may be added to morphine.

Lignocaine, magnesium and zinc have been described with limited efficacy.

Two well-described and effective adjuvants are:
Ketamine
Dexmedetomidine/clonidine

A regime used successfully in eThekwini-Durban is:

Total PCA reservoir volume: 50–100 ml
PCA volume: 0.5 ml
Lockout: 5 minutes

PCA dose:
Morphine 1–2 mg
Ketamine 2–4 mg
Dexmedetomidine 1–2 mg

Should morphine be used as a sole agent, a reservoir of 100 ml is appropriate.

When adjuvant ketamine and dexmedetomidine are used as adjuvants, weaning that has proved effective is as follows:

Initial (in 50 ml):
Morphine 100 mg
Ketamine 400 mg
Dexmedetomidine 200 mcg

Change
Morphine 100 mg
Ketamine 200 mg

Final
Morphine 100 mg

Morphine PCA dose in 48 hours averaged for 24 hours can be used to calculate opioid requirements as follows:

1. Morphine: 0.3 x total
2. Oxycodone: 0.6 x total

The oral dose is then divided as follows:
Long-acting: 8–12 hourly: 70%
Short-acting: 2–4 hourly: 30% (5–10% of long-acting dose)

Sub-lingual fentanyl[13]

Fentanyl as a sublingual film bypasses the stomach and thus delayed absorption in the duodenum. There is also no liver metabolism.

Absorption is directly into the well-perfused buccal mucosa giving an onset time of 5 minutes, closely coinciding with that of the cancer pain.

The duration of action is 60 minutes, also coinciding well with the duration of cancer pain.

Concerns regarding opioid addiction[14]

Clinicians treating acute pain are understandably concerned that their opioid prescriptions may lead to addiction. This concern is largely misplaced, as addiction requires activation of the dopamine reward pathway, which is inhibited by acute pain. Clinically, patients who are on chronic opioids will develop acute sedation and respiratory depression when given an effective local anaesthetic block. Patients who receive opioids for injury can stop taking these drugs after resolution of the injury without withdrawal symptoms. Finally, simple risk assessment of patients should be done prior to prescribing opioids. The most important risk factor for development of addiction to prescription opioids is the addiction to other substances, particularly alcohol, cocaine, amphetamines and opioids (illicit and prescription).

Prescription opioid addiction also appears to be a major problem in the USA, due to unique social and medical factors, while addiction is a much less significant problem in the rest of the world, particularly Canada, just across the border from the USA.

New Zealand has a rigorous assessment process for the inclusion of drugs on their national pharmaceutical schedule by a body called PHARMAC. The New Zealand schedule has endorsed oxycodone for acute pain management with no increase in addiction.

Conclusion

While recognising that the management of pain needs to be tailored to the individual patient's needs, cost effective, evidence-based protocols should be instituted to guide pain management of acute and chronic pain. These protocols, incorporating the principles of multimodal analgesia and Enhanced Recovery After Surgery (ERAS) should be extensively discussed prior to implementation with ongoing training and mentorship to ensure compliance.

Acute pain services are unlikely to become a feature of South African public or private hospitals but appropriate application of simple interventions should not only result in improved patient satisfaction, and possibly outcomes, but a reduced, rather than increased, workload for the increasingly stressed surgical nurses.

Adequate, safe pain relief is a fundamental human right that can be provided to benefit patients and improve the satisfaction of both patients and staff.

Essential resources

1. South African guidelines for the management of acute pain (free download): http://www.sajaa.co.za/index.php/sajaa/issue/view/64
2. South African Cancer Pain Working Group. Guide to the Treatment of Cancer Pain in South Africa (free download). https://painsa.org.za/guide-to-the-treatment-of-cancer-pain-in-south-africa/

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