Pain management in palliative care - choice of analgesia

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Educational aims

- To provide an overview of common analgesia used in the management of cancer pain
- To provide a basic understanding of the pharmacology of these drugs and their place in therapy

Keywords
pain, opioids, analgesia,cancer

Pain occurs in 40 to 80% of patients with advanced progressive disease.[1] Despite the publications of various guidelines and research in this area together with an extensive choice of analgesia, pain management still presents a challenge in everyday practice. Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage[2] or in simpler terms "pain is what the patient says hurts."

Pain can be classified broadly into two categories, nociceptive and neuropathic, characterised by different clinical presentations and underlying pathophysiological mechanisms. (Table 1)

The WHO analgesic "ladder"

The WHO guidelines were first published in 1986 and are considered to be the gold standard for managing pain in advanced cancer.[3] Figure 1 gives a schematic diagram of the recommended "analgesic ladder"

Non-opioids include non-steriodal anti-inflammatory drugs (NSAIDs), paracetamol and adjuvant analgesia. Adjuvant drugs include antidepressants, anticonvulsants, antispasmodics, steroids and bisphosphonates.

Choice of analgesia

Non-opioid

- Paracetamol
  Despite being a widely used drug and available for a very long time, the mechanism of action for paracetamol still remains unclear. The standard explanation is that it acts as a cyclo-oxygenase inhibitor in the brain, explaining both its analgesic and its antipyretic properties.[4] It is also thought to be involved with serotonin modulation pathways. Ultimately paracematol remains a safe, well tolerated and effective drug especially in the management of mild to moderate pain. It can also be administered with other analgesia to achieve an additive effect. The main problem is hepatotoxicity especially in overdose.
- Non-steroidal anti-inflammatory drugs (NSAIDs)
  NSAIDs are useful in treating mild to moderate pain mediated by prostaglandins, which serve to sensitise nociceptors.[5] They are of particular benefit for pains associated with inflammation. In spite of insufficient evidence, NSAIDs have traditionally been used in the palliation of metastatic bone pain although radiotherapy remains the treatment of choice.[6]
  NSAIDs inhibit cyclo-oxygenase (COX), an important enzyme in the arachidonic acid cascade which results in the production of tissue and inflammatory prostaglandins. COX exists in two forms. COX-1 is "constitutive" i.e is part of the body's normal physiological constitution with near constant levels and activity in most tissues, including the central nervous system (CNS). COX-2 expression is generally low or non-existent but is "inducible" i.e. is massively produced within a few hours by inflammation.[7] The main exceptions to this are parts of the central nervous system (CNS), kidneys and seminal vesicles which contain high levels of COX-2 (Figure 2).
  Non-specific COX inhibitors, such as aspirin, ibuprofen, diclofenac and naproxen inhibit both isoenzymes to produce analgesia. However this also leads to adverse effects typically observed as gastrointestinal and renal toxicity.

Opioids

Opioids include all drugs that act at opioids receptors, (mu, kappa, delta and ORL-1), distributed in varying densities throughout the body, particularly in the nervous system. Agonism at these receptors produces analgesic effects observed with opiates.

Codeine is usually the drug of choice for mild to moderate pain (step 2, WHO analgesic ladder). Its analgesic effect is largely due to its metabolism to morphine by cytochrome CYP2D6. Codeine is considered one tenth as potent as morphine. As a general rule, products containing less than 30mg of codeine per dose are not suitable step 2 analgesia. Although classified as a weak opioid, patients taking codeine still present with typical opioid adverse effects including nausea, vomiting, sedation and constipation. However, unlike morphine weak opioids have a "ceiling dose",

Table 1. Mechanism of pain and implications for treatment

Type of pain	Mechanism	Examples	Typical treatment
Nociceptive			
Muscle spasm	Stimulation of nerve endings	Cramp	Muscle relaxants
Somatic		Soft tissue, bone pain	NSAIDs ± opioid
Visceral		Liver capsule pain	
Neuropathic			
Nerve compression Nerve injury De-afferentation pain Central pain	Pain transmitted from damaged neural tissue in either the peripheral or central nervous system	Neuroma or nerve infiltration eg brachial or lumbosacral plexus Spinal cord compression	Opioid + corticosteroid Opioid, NSAID, tricyclic antidepressant, anti-epileptic, NMDA-receptor-channel blocker, spinal analgesia

Adapted from Twycross R. Introducing Palliative Care, 4th Edition, Radcliffe Medical press 2003

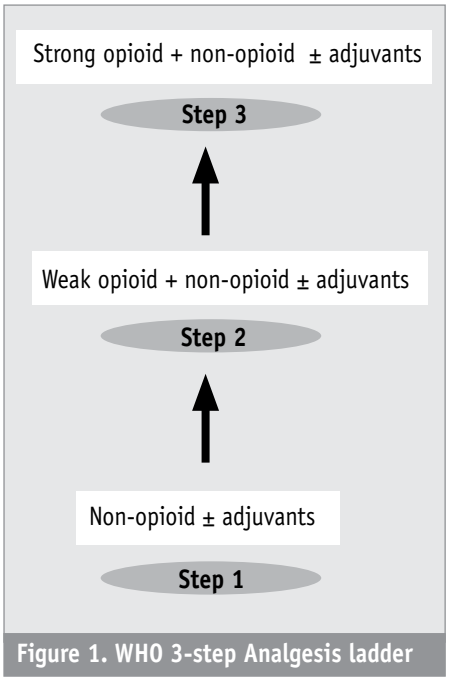
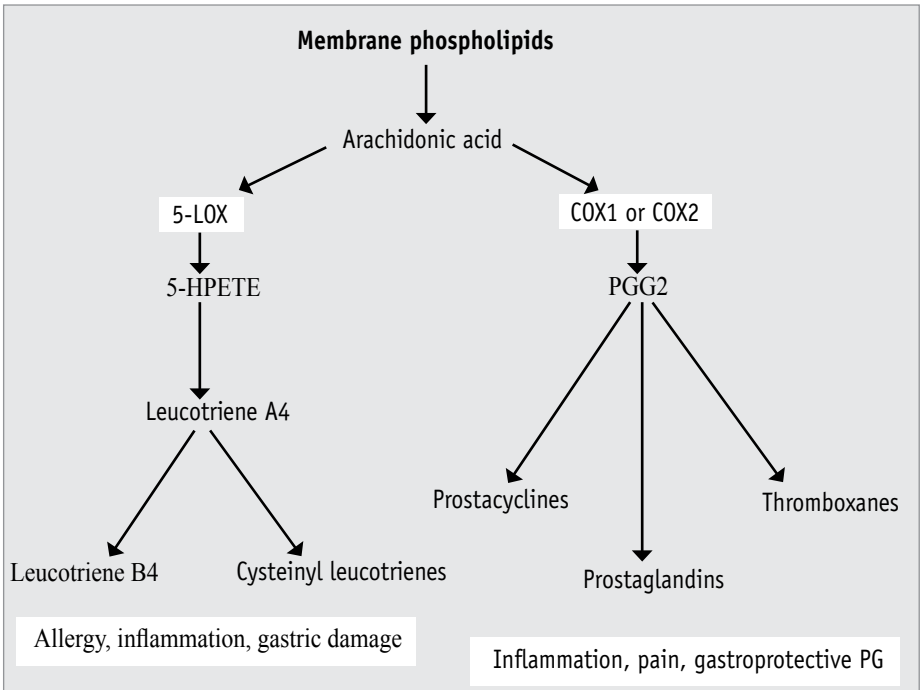


Figure 1. WHO 3-step Analgesis ladder

Table 2. Commonly prescribed adjuvant analgesia in the management of caner pain.

Indication	Drugs
Neuropathic pain	Amitriptyline, gabapentin, clonazepam, dexamethasone
Neuropathic pain (unresponsive to the above)	Ketamine
Bowel obstruction	Hyoscine butylbromide, octreotide
Metastatic bone pain	Pamidronate, zolendronate, dexamethasone

Adapted from Twycross R et al. Palliative Care Formulary, Third edition, 2007



Key: COX – cyclo-oxygenase, 5-HPETE – hydroperoxyeicosatetraenoic acid, LOX – lipoxygenase, PG- prostaglandin
Non-specific COX inhibitors, such as aspirin, ibuprofen, diclofenac and naproxen inhibit both isoenzymes to produce analgesia. However this also leads to adverse effects typically observed as gastrointestinal and renal toxicity.

Figure 2. Products of arachidonic acid metabolism involved in inflammation

above which any increase in analgesia is outweighed by progressively more adverse effects. For codeine, this is typically 240mg over 24 hours. When the ceiling dose has been reached, step 3 treatment should be introduced.[8]

Morphine remains the drug of choice for moderate to severe pain (step 3, WHO analgesic ladder). It is a potent mu receptor agonist. The liver is the predominant site of metabolism where it is converted to two main forms: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G produces potent opioid effects whereas the pharmacology of M3G remains unclear. Both metabolites are renally excreted so patients with renal failure are at a greater risk of opioid toxicity.

The starting dose of morphine depends on whether or not the patient has been previously exposed to opioids and at which dose. For opioid-naïve patients, an immediate release formulation should be prescribed and the dose of morphine titrated according to response. Typically, 5 to 10mg every four hours is used with the option for further doses if the pain is not controlled with four hourly dosing. Once the morphine requirement over 24 hours is established, slow release preparation may be prescribed. The patient should be advised to expect sedation, nausea and vomiting during the titration period although tolerance develops with these adverse effects. However, tolerance does not develop to constipation and regular laxatives should be prescribed.

It has long been observed anecdotally that patients who develop intolerable adverse effects to morphine while achieving inadequate analgesia may sometimes benefit from switching to an alternative opioid.[9] The initial dose of the second opioid depends on the relative potency of the two drugs. This again is a huge area of controversy and any equianalgesic tables should be considered with caution as there is lack of comprehensive data and inter-patient variation. Special caution should be exercised when converting a patient from high dose morphine to another opioid as the recommended equivalent doses become progressively less accurate as the dose increases. Therefore, when converting at high dose, it is best to give lower than the calculated equivalent doses and rely on "as required" doses to make up any deficit while re-titrating to a satisfactory dose of the new opioid. Some examples of alternative opioids are discussed below.

Oxycodone is a stronger opioid than morphine. Oxycodone is one and a half to two times more potent than morphine. Its opioid receptor site affinities remain controversial but apart from μ receptor activity it is thought to have agonist effects on receptors as well.[10] It is better tolerated than morphine especially in patients experiencing hallucinations.

Similarly fentanyl is a stronger opioid than morphine. It has a low molecular weight and is lipophilic making it suitable for transdermal and oral transmucosal administration. Fentanyl patches are applied to the skin for 72 hours and a reservoir of fentanyl is formed in the fatty tissue under the skin. Analgesia is not achieved for at least 12 hours after the first patch is applied and steady state may not be achieved for up to 48 hours so analgesic benefit should not be assessed until three days after the first patch is applied. Once steady state is attained, the plasma half life can be up to 25 hours. Transdermal fentanyl can be considered an option for patients with renal impairment, severe constipation, dysphagia or bowel obstruction.

Methadone is reserved for patients with pain refractory to conventional treatment due to its complicated pharmacokinetics which can lead to accumulation. There is a lack of potency ratio between methadone and morphine and it should only be initiated by specialists in pain management. One major advantage is that methadone is also an N-methyl-D-aspartate (NMDA)-receptor channel blocker in addition to opioid agonism and has benefits in managing neuropathic pain.

Practice points

- Pain is still one of the commonest symptom experienced by cancer patients, however it can be managed well in the majority of patients if the correct analgesia and appropriate dose escalations are used.
- The WHO analgesic ladder remains the gold standard for managing pain.
- NSAIDs have traditionally been used in metastatic bone pain, although evidence in this setting is limited. Radiotherapy remains the treatment of choice and these patients should be referred to oncology/palliative services to ensure best management.
- Patients should be counselled on adverse effects of opioids and appropriate medication prescribed to avoid preventable adverse effects.

Adjuvant analgesia

Adjuvant analgesia tend to be drugs that are licensed for indications other than pain. Hence they are not primarily classified as analgesia even though they may relieve pain that is usually not responsive to standard analgesia. These include steroids, anti-depressants, anti-epileptics, bisphosphonates and antispasmodics. Commonly prescribed adjuvant analgesia are listed in Table 2.

The choice of drugs depends on type of pain (nociceptive or neuropathic), co-existing morbidity and current medication. Adjuvants can also have opioid sparing effects and the opioid dose should be reviewed when initiating adjuvant analgesia. There is a risk of additive toxicity from polypharmacy, as adjuvant analgesia are typically administered to patients who are receiving several other drugs. The potential for additive side-effects must be considered prior to prescribing. The decision to add or continue a treatment must be based on a careful assessment of outcomes and a clear understanding of the goals of care.

Conclusion

Pain is one of the commonest symptoms of advanced cancer and probably the most dreaded by patients. However, the majority of patients with cancer pain can be well managed as long as analgesia is used appropriately and assessed regularly. Many patients are frightened of opioids, particularly morphine due to its possible connotations with death. It is vital to explore their fears before starting the drug and ensure that support is provided. Strategies should be in place to manage side effects as most can be easily managed but can have devastating effects if ignored or not addressed appropriately.

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