



Global Year Against Cancer Pain

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Pharmacological Management of Cancer Pain

Cancer pain involves different types of pain (tissue injury and inflammation, neuropathic pain, and visceral pain), and it is often aggravated by anxiety and depression. All components need to be considered in the management of cancer-related pain.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- NSAIDs are effective in tissue injury and inflammation. They are particularly beneficial in pain due to bone cancer or metastasis because of their anti-inflammatory effect and because they may decrease tumor growth.
- NSAIDs should be used either alone, or in combination with opioids if they are not effective enough on their own.
- NSAIDs should not be used if the patient is allergic to them, and their use should be considered with great care if there is a risk for gastrointestinal irritation or bleeding, decreased kidney function, heart failure, or bleeding due to decreased platelet function. Elderly patients are particularly vulnerable to all adverse effects.
- Gastric protection should be considered, particularly if the patient is receiving other drugs that may cause damage to the gastric mucosa (e.g., corticosteroids).
- Cyclooxygenase-2 (COX-2)-selective NSAIDs cause somewhat less gastric irritation, and they do not decrease platelet function. Other adverse effects are similar to those of nonselective NSAIDs. COX-2-selective NSAIDs are no more effective as analgesics compared with nonselective analgesics.
- Paracetamol (acetaminophen) can be considered when NSAIDs are contraindicated. It is a less effective analgesic than NSAIDs.

Opioids

- Opioids are usually added to NSAIDs or paracetamol (acetaminophen).
- *Weak opioids* (e.g., codeine, tramadol) can be used only if pain is moderate, because they have a maximum recommended dose after which the adverse effects increase more than the analgesic effect.
- About 10% of patients are unable to metabolize either codeine or tramadol to the active opioid metabolite (morphine or M1). In these patients, these drugs have poor efficacy or none at all.
- *Strong opioids* (e.g., morphine, oxycodone, hydromorphone, fentanyl, and methadone) differ from weak opioids in having a much broader dose range. If the pain is opioid sensitive (it can be relieved by an opioid), a greater effect can be achieved by increasing the dose.
- *Long-acting opioids* (controlled-release or slow-release) are used for stable or baseline pain. They are usually administered twice daily by mouth.
- *Fast- and short-acting opioids* are used for breakthrough or incident pain when needed (via oral, transmucosal, or inhaled routes of administration).
- *Respiratory depression* is rarely a problem because pain stimulates the respiratory center, and tolerance develops to this adverse effect.
- *Nausea and vomiting* may be a problem, particularly at the beginning of treatment. Nausea is treated with haloperidol, with metoclopramide (if there is also gastric stasis), or with 5-HT₃-antagonists (if opioids have also caused severe constipation).
- *Constipation* is a common and persistent adverse effect because opioids regulate bowel function. Increased absorption of water causes hard stools, which can be treated with osmotic stool softeners. Opioids also cause spasm of the bowel, necessitating treatment with stimulant laxatives. Opioid antagonists (e.g., methylnaltrexone) that do not penetrate the blood-brain-barrier are a new effective treatment for opioid-induced constipation.

- *Sedation, dysphoria, hallucinations, and nightmares*, as well as *sweating and itching*, are other opioid-related adverse effects.
- *Addiction* is rarely a problem because the context protects against it when opioids are used to control pain from cancer, which is potentially a life-threatening condition.
- Development of *physical dependence* is typical for opioids, which should never be abruptly discontinued, so as to avoid *withdrawal* symptoms.
- Development of *tolerance* is typical for opioids. Pain itself may decrease the development of tolerance, but increasing pain will also necessitate dose escalation. Tolerance can be dealt with by increasing the dose; by changing the opioid (cross-tolerance is not complete); by changing the route (spinal administration); or by adding other drugs, such as ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, or clonidine, an α_2 -adrenergic agonist. Methadone can be particularly effective when tolerance has developed to other opioids, perhaps because of its non-opioid effects (e.g., it has a weak NMDA-antagonistic effect). Because of its difficult pharmacokinetics, methadone is not a first-line opioid.
- All commonly used opioids are *mu-opioid receptor agonists*, but they have *different pharmacokinetic profiles* (bioavailability, metabolism, passage through the blood-brain-barrier, and excretion).
- The preferred *route of administration* is by mouth. Transdermal fentanyl can be considered if pain is stable and the required opioid doses are moderate. Transdermal absorption of fentanyl is impaired in cachectic patients. Subcutaneous administration by continuous infusion can be considered if the patient cannot take medications by mouth. Other drugs (e.g., antiemetics) can be added to subcutaneous infusions of morphine, oxycodone, or hydromorphone.
- *Spinal* (epidural or subarachnoid) opioid administration can be considered when less invasive methods are not effective. Local anesthetic agents and clonidine will increase the efficacy of opioids.

Other Drugs

- *Antidepressants* can be used to treat both depression and neuropathic pain. Antidepressants have been specifically studied in cancer-related pain only in postmastectomy syndrome (tricyclics were effective) and in chemotherapy-induced neuropathic pain (tricyclics were not effective). If the patient has both neuropathic pain and depression, a drug should be selected that can relieve both (e.g., dual-action antidepressants that inhibit the uptake of both norepinephrine and serotonin).
- *Anticonvulsants* can be used to alleviate neuropathic pain. Gabapentin and pregabalin have been studied in cancer-related neuropathic pain (the drugs were effective) and in chemotherapy-induced neuropathic pain (the drugs had no effect), and they are currently being studied in bone cancer pain. Gabapentin and pregabalin have anxiolytic effects that may be useful in cancer pain.
- *Corticosteroids* reduce edema and inflammation and stabilize nerve membranes. They can be useful in pain due to edema (e.g., in the brain, spinal cord, or liver). They also alleviate nausea and increase mood and appetite.
- *Ketamine* is an NMDA-receptor antagonist that has been used in subcutaneous or intravenous infusions to alleviate opioid-induced hyperalgesia and tolerance. It can be given by mouth, but its oral bioavailability is low and variable.

