Pain

KEY POINTS

- Pain is common in patients with advanced cancer, with at least 66% of individuals experiencing pain
- Most pain can be satisfactorily controlled using simple medications, following the World Health Organization (WHO) Guidelines
- The WHO three-step analgesic ladder provides guidance about how best to treat pain in adults and adolescents
- The WHO method includes 4 key principles: "**by mouth**", "**by the clock**", "**for the individual**", and "**with attention to detail**"
- Acetaminophen/paracetamol and NSAIDs can be used for mild pain
- Opioids such as morphine should be used for moderate to severe pain
- Remember to prevent or treat the side effects of morphine, such as constipation and nausea/vomiting, whenever prescribing opioids

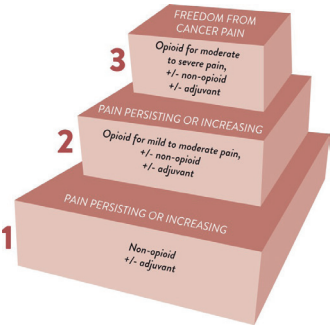

Image Reference: World Health Organization. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents.

- There is no maximum dose for strong opioids, including morphine – the correct dose is the dose that relieves the individual's pain
  - When increasing the dose of opioids, monitor for opioid-induced neurotoxicity, which can occur with rapid opioid titration, particularly in patients whose pain is only partially responsive to opioids
- Signs of opioid-induced neurotoxicity include myoclonus, hyperalgesia, delirium, allodynia (pain from a non-painful stimulus such as light touch), tremors, seizures, and hypersomnolence

- Neuropathic pain is common, as is pain which is transmitted by a damaged nervous system
- Consider the use of adjuvant medications at all levels of the analgesic ladder (especially with neuropathic pain)
- Pain that is poorly managed initially can lead to difficult-to-treat neuropathic pain syndromes and other symptoms

- Infants and children experience pain as much as adults, and it is common in advanced cancer and in other severe life-threatening diseases
- Pain receptors are mature (and inhibitory systems are immature) at birth, therefore infants and newborns do feel pain (perhaps even more so than adults)
- Pain suffered by children with life-limiting diseases may have considerable effects on both the child, their family, and the healthcare team

ASSESSMENT

- A good clinical assessment is important to try and identify the underlying cause of the pain (e.g. tumour involvement, bone metastases, liver enlargement, etc)
- Listening to the patient describe their pain location, intensity, quality, "what makes it worse", "what makes it better" can tell a lot about what might be causing the pain and how best it might be treated
- The use of pain measurement scales such as the Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) are important tools to use in assessing a patient's pain and the response to treatment
- Asking about the impact of pain on the person's function and sleep is important
  - Asking about the impact of pain on the person's ability to complete the activities of daily living, such as dressing, bathing, eating meals, and ambulating, can help to assess the impact of

the pain for the individual patient

- Consider whether radiological investigations will be helpful
  - X-rays can help to determine if bone metastasis are present
- Assess for the presence of neuropathic pain, which may be suggested by the following:
  - Pain may be described as stabbing, burning, or shooting
  - Allodynia or hyperalgesia may accompany the pain
    - Allodynia – a sensation that is not expected to be painful causes pain (e.g. light touch of clothing on the skin)
    - Hyperalgesia – an increased sensitivity to feeling pain and an extreme response to pain

- A quiet, sleeping child may be exhausted and withdrawn but may still be in pain
- Children may not report pain because they do not want to be thought of as "bad" or because they fear what might happen next (e.g. they will receive a painful injection)
- Children may be able to use distraction to reduce their pain, but they may still be in pain (e.g. playing or watching videos)
- Even young children (3-4 years and older) can self-report their pain
- Several pain assessment tools based on age, development, and ability to communicate have been developed and should be used to facilitate an assessment of pain severity and give children a voice in their treatment

MANAGEMENT

- Consider treatment of the underlying cause (e.g. oncological treatment of tumour, radiation for bone metastasis, etc.)

Consider if the patient is well enough to benefit

FOR MILD PAIN

- **Paracetamol/acetaminophen 325-1000 mg PO/IV q4-6**h (daily maximum 4 g/day)
- **Paracetamol/acetaminophen** can be combined with NSAIDs

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Consider using topical NSAIDs if these are available, e.g. **diclofenac topical cream (1.5-5%) applied to affected area QID**; do not use on open wounds
  - The peak analgesic effect occurs within 1-2 hours
  - Use with caution, particularly in patients with increased risk of GI or renal toxicities as serious side effects can include GI bleeding, renal toxicity, and congestive heart failure
- If GI bleeding occurs, NSAIDs should be discontinued
- The risk of GI toxicity can be reduced by the addition of a protective agent such as an H2-antagonist (e.g. famotidine) or a proton-pump inhibitor (e.g. omeprazole)
- There is no evidence to show that any particular NSAID is more effective than another one
- Note that selective COX-2 inhibitors (celecoxib, meloxicam) do not affect platelet function, and therefore do not increase bleeding risk

Examples of common non-selective NSAIDs include:

- **Ibuprofen 200-400 mg PO q6-8h**
- **Diclofenac 50 mg PO/Subcutaneous TID**
- **Naproxen 250-500 mg PO/PR BID**
- **Ketorolac 10 mg PO QID or 10-30 mg Subcutaneous TID**

FOR MODERATE PAIN

- **Morphine (PO, 5-10 mg q4h)** should strongly be considered as the first-line treatment for moderate pain, since recent evidence suggests that strong opioids (such as morphine) are a more effective

treatment for moderate cancer pain than weak opioids

- Weak opioids (e.g. codeine and tramadol) can be used for moderate cancer pain, when morphine is not available
  - e.g. **codeine 30 mg q4h PO or tramadol 50-100 mg PO QID**
  - Codeine is often combined with other agents such as acetaminophen/paracetamol and thus maximum doses may be limited by the amount of acetaminophen/paracetamol
  - Codeine is a prodrug which requires conversion to morphine in the liver in order to provide analgesia
    - The rate of this conversion varies widely between individuals, which leads to significant variation in the analgesic response
- Combine opioids with NSAIDs and adjuvants to achieve the best possible pain control

FOR SEVERE PAIN

- Morphine or another strong opioid should always be the first-line treatment, provided that opioids are available
- The initial starting dose will depend on the patient's previous exposure to opioids:
- **Morphine 5-10 mg PO q4h regularly (or 2-5 mg Subcutaneous/IV)** and a breakthrough or rescue dose every 4 hours, as required (see Appendix 1), is suitable for an opioid-naive patient or patients who have already been taking a weak opioid
- Titrate the regular dose to achieve good control (more than 3 breakthrough doses per day often means that the baseline morphine dose is too low)
- Calculate the new dose of morphine by adding the amount of breakthrough morphine being used in 24 hours and the regular total daily dose. The total is then divided by 6 to determine the new q4h dose
- If pain is poorly controlled, increasing the opioid dose by 25-50% is appropriate. Generally, this is done every 2-3 days for outpatients,

and 1-2 days for inpatients

- There is no maximum dose for morphine and other strong opioids: the correct dose is the dose that provides the individual with adequate analgesia in the absence of unwanted side effects
- Alternative routes for morphine include PO, subcutaneous, buccal, IV, and via gastrostomy tube – the enteral route is generally preferred, provided that the patient is able to swallow. If the patient is unable to swallow, then subcutaneous is the preferred route
- The PO: Subcutaneous morphine ratio is 2:1
- The PO: IV morphine ratio is 2-3:1
  - e.g. 10 mg oral morphine = 5 mg Subcutaneous morphine
- Be aware, educate patients/families about how to prevent and treat the common side effects of morphine:
  - Constipation: always prescribe laxatives/stool softeners when starting someone on opioids, see Constipation section
  - Nausea is generally temporary and associated with initiating opioids or dose change, ensure that antiemetics are prescribed especially when starting someone on opioids
  - Excessive sedation or drowsiness after starting opioids is generally temporary, lasting 1-2 days
    - Patients may sleep more after starting morphine if their pain was previously poorly controlled and prevented them from sleeping well, and families should be counselled about this when opioids are being initiated

NEUROPATHIC PAIN

- Patients with signs and symptoms of neuropathic pain should be managed following the three-step ladder of analgesic management as described above
- Opioids are first-line medications for treating neuropathic pain and should be used in combination with adjuvants (see below), such as a tricyclic antidepressant or anticonvulsants
- Other adjuvants such as NMDA receptor antagonists (e.g. ketamine) and

antiarrhythmic agents (e.g. lidocaine) are not routinely used as first-line medications, but are sometimes tried by clinicians with experience/skill in the use of these agents

ADJUVANTS

- Adjuvants are medications or measures that provide pain relief when administered in combination with opioids
- They are often used for pain from bone metastases and neuropathic pain
- **Bisphosphonates** can be used to prevent and treat bone pain
  - NSAIDs, corticosteroids, and radiotherapy are additional therapies which can be considered for bone pain
- For neuropathic pain, consider a trial of **tricyclic antidepressants**, starting with a low dose and increasing every 3-5 days if tolerated (e.g. **nortriptyline, amitriptyline**)
- Serotonin and norepinephrine reuptake inhibitors (SNRIs) can also be used for neuropathic pain, but evidence for their efficacy is more limited. Common examples are **duloxetine** or **venlafaxine**
- Gabapentinoids (**gabapentin** or **pregabalin**) are also useful adjuvants

- Morphine is the main analgesic for children with severe life-threatening or life-limiting conditions who have moderate or severe pain
- Weak opioids are not recommended due to concerns about safety, because of the wide variations in codeine and tramadol metabolism between children, and the immaturity of their liver metabolism for these medications

FOR MILD PAIN

- **Paracetamol/acetaminophen/ 10-15 mg/kg PO/IV q4-6h (Maximum: 75 mg/kg/day or 4000 mg/day)**
  OR
  Ibuprofen:
  <6 months: 5 mg/kg/dose PO q8h
  >6 MONTHS: 5-10 mg/kg/dose PO q6-8h
  (Maximum: 40 mg/kg/day or 2400 mg/day)
  OR
  Naproxen: 5-10 mg/kg/dose PO q12h
  (Maximum: 1000 mg/day)
  OR
  Ketorolac
  – PO: 1 mg/kg/dose PO q4-6h PRN (Maximum: 40 mg/day)
  – IV: 0.2-0.5 mg/kg/dose IV q6-8h PRN (Maximum: 120 mg/day)

  Usual duration of therapy is 48 to 72 hours and should not exceed 5 days of total treatment (oral and injectable) in order to minimize the risk of adverse cardiovascular and gastrointestinal side effects
  OR
- **Diclofenac**
  6 months to 12 years: 1-1.5 mg/kg/dose PO BID or 0.7-1 mg/kg/dose PO TID (Maximum: 50 mg/dose); 0.5-1 mg/kg/dose PR q8-12h PRN, (Maximum: 100 mg/day)

FOR MODERATE TO SEVERE PAIN

- **Morphine**
  Starting doses for opioid-naive patients:
  Less than 6 months of age:
  – PO/SL: 0.05-0.1 mg/kg/dose q4h
  – IV/Subcutaneous: 0.025 to 0.05 mg/kg/dose q2-4h

- **Greater than 6 months of age:**
  - **PO/SL: 0.2-0.3 mg/kg/dose q4h, (Maximum starting dose: 10 mg)**
  - **IV/Subcutaneous: 0.05-0.1 mg/kg/dose q2-4h, (Maximum starting dose: 5 mg)**

- **Continuous IV/Subcutaneous Infusion:**
  - **Start at 20-40 mcg/kg/hr and increase incrementally by 10 mcg/kg/hr**

- Codeine: DO NOT USE in children

- **Tramadol DO NOT USE in children, unless no other opioids are available**

  Risk due to high variation in liver metabolism and risk of serious harm

  1-2 mg/kg/dose PO/IV q4-6h (Maximum: 100 mg/dose, 400 mg/day

ADJUVANTS

- **Amitriptyline 0.1-0.5 mg/kg/dose PO nightly, (Maximum starting dose: 10 mg). May increase by 0.1-0.2 mg/kg/dose every 5-7 days to a max of 2 mg/kg/day (Maximum: 150 mg/day)**

  Monitor closely for anticholinergic side effects (e.g. constipation, dry mouth, drowsiness, blurry vision). Important to note potential drug-drug interactions with other drugs metabolized by CYP2D6

- **Gabapentin**
  Starting dose of 5 mg/kg/dose PO daily x 3 days, followed by 5 mg/kg/dose PO BID x 3 days, followed by 5 mg/kg/dose PO TID; (Maximum starting dose: 300 mg); usual dosing range of 15-60 mg/kg/day (Maximum dose: 3600 mg/day)

Management of Respiratory Depression Related to Opioids

- Inappropriate high doses of opioids may lead to respiratory depression (low respiratory rate and shallow respirations), apnoea, and respiratory arrest
- Opioids do not cause respiratory distress
- If respiratory depression occurs following a dose of opioid medication, naloxone should be administered
- Stepwise titration should be used to avoid acute and sudden physical pain and opioid withdrawal
- **Naloxone 40 mcg/dose IV/IM/Subcutaneous, given every 2-3 mins until respiratory depression is reversed**
- Further doses of naloxone are likely to be required every 30-60 minutes until the effect of the opioid has worn off (e.g. 4 hours for oral morphine)
- Naloxone will also cause opioid-related analgesia to be reversed and can precipitate a pain crisis

PITFALLS/CONCERNS

- Avoid using pethidine/meperidine (an opioid) in palliative care, since ongoing use leads to accumulation of its neurotoxic metabolite (normeperidine) which causes delirium and seizures
- Never ever use a slow-release opioid for breakthrough pain (use regular short-acting opioids instead)
- Serious side effects can occur with NSAIDs – they should be used with caution

- Children less than 6 months are more sensitive to opioid-induced respiratory depression and therefore need lower initial doses
- Codeine is NOT recommended for children due to the risk of rapid metabolism, which can lead to overdose and death
- Urinary retention and pruritus (as a side effect of opioids) are more commonly seen in children compared to adults

PALLIATIVE TIPS

- Treat pain promptly and aggressively
- The relief of psychological, social, and spiritual distress is also important; attempting to relieve pain without addressing the patient's non-physical concerns is likely to lead to frustration and failure
- Constant pain requires regular (around the clock) analgesia to relieve and prevent pain
- Make sure there is a breakthrough or rescue dose (BTD) in addition to the regular dose of morphine or other opioid
- Optimise pain control by increasing the dose of opioids in a gradual step-wise manner, until the pain has improved
- The PO morphine to Subcutaneous/IV morphine ratio is 2:1, e.g. 10 mg oral = 5 mg Subcutaneous/IV
- Remember to use adjuvants in the treatment of pain

- Children have less distress when they can understand what is happening and are involved in their symptom management
- Play, music, and games can be very helpful in association with the pharmacological methods as described above

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