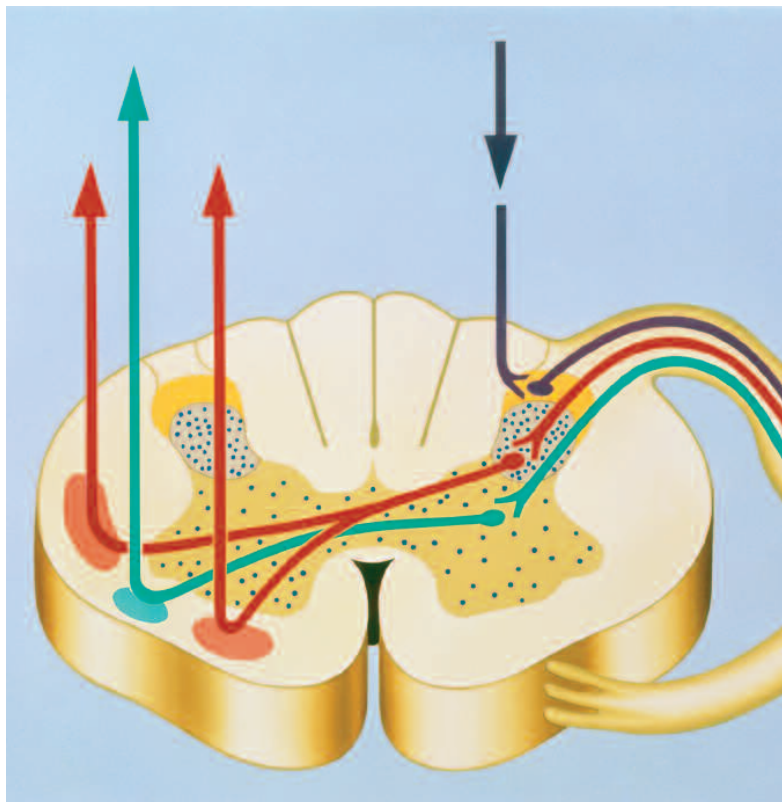


Managing post-operative pain

In the eighth article of a series on peri-operative care, **Mohamed H. Rahman** and **Jane Beattie** focus on the physiology of pain and briefly describe the non-opioid and opioid analgesics used for post-operative pain relief



John Bavos/SPL

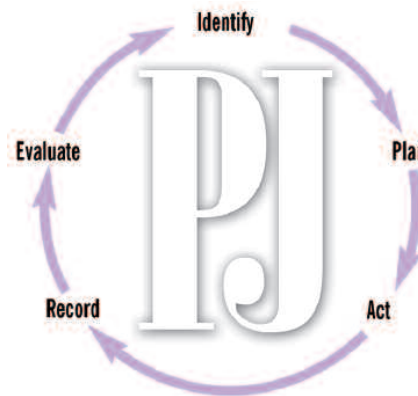
Pain perception is a balance between noxious impulses travelling into the spinal cord and inhibitory impulses within the spinal cord

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage. Pain is usually protective — it warns of tissue damage and prompts treatment — but post-operatively it can delay recovery. Factors affecting the degree of post-operative pain include the patient's previous experiences and mental preparation (which can be influenced by the information given by the surgeon and anaesthetist), intra-operative pain management, the nature and duration of surgery (eg, laparoscopic surgery minimises post-operative pain), the site and size of the incision and the extent of surgical trauma. Short incisions that remain within one dermatome (an area of skin receiving sensation from a nerve entering a single nerve root of the spinal cord) are less painful than those that cross several nerve distributions. Pain tolerance differs between individuals and insomnia, anxiety or depression all lower tolerance.

Physiology

Surgical tissue damage causes local release of algogenic substances, such as bradykinin, arachidonic acid, histamine, 5-hydroxytryptamine (5HT), substance P and prostaglandin. These

Inadequately controlled pain causes morbidity



Identify knowledge gaps

1. What are the possible consequences of poorly controlled pain in a post-operative setting?
2. What is the WHO analgesic ladder?
3. What are the modes of action and adverse effects of commonly prescribed analgesics?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education) and at www.uptodate.org.uk. This article relates to "clinical pharmacy".

chemicals stimulate peripheral pain receptors (nociceptors), which transmit impulses via afferent nerve fibres to the spinal cord. The large, fast-transmitting nerve fibres are myelinated A δ fibres, stimulation of which produces rapid sharp localised pain ("pricking"). Stimulation of slower, non-myelinated C fibres produces dull aching and poorly localised pain.

These fibres end in the dorsal horn of the spinal cord where they synapse with second order neurones, which ascend to the midbrain (thalamus and other nuclei). Fibres from the thalamus are then relayed to the sensory cortex where pain signals are appreciated as coming from a specific body site. Panel 1 (p146) describes the modulation of pain impulses.

Endogenous opiates When pain signals reach the brain stem and thalamus, the periaqueductal grey matter and nucleus raphe magnus release endorphins and enkephalins, which inhibit pain transmission in the spinal cord. Seventy per cent of endorphin and enkephalin receptors are on the presynaptic membrane of afferent neurones so much of the pain signal is modulated before it activates the dorsal horn. For example, dynorphin activation of receptors on inhibitory interneurons causes the release of gamma-amino

Complications of post-operative pain

Inadequately controlled pain causes morbidity. The cellular response to pain and surgical tissue damage causes proteins to break down, platelets to aggregate and the immune system to be suppressed. Pain can also cause ileus, nausea and vomiting. Tachycardia and hypertension occur with the release of catecholamines and this can lead to myocardial ischaemia or infarction.

Diaphragmatic splinting and impaired intercostal muscle function resulting from the pain of an upper abdominal or thoracic wound results in a reluctance to breathe deeply. This causes a weak cough, sputum retention, atelectasis, hypoxia and pneumonia. Hypoxia slows deposition of collagen and delays wound healing.

Reduced mobility, secondary to pain, can lead to increased incidence of deep vein thrombosis and pulmonary embolism or the development of pressure sores. Additional complications of inadequately controlled pain include restlessness, anxiety and impaired sleep.

butyric acid (GABA). This results in hyperpolarisation of the dorsal horn cells and inhibits transmission of the pain signal

Treating post-operative pain

Post-operative pain is usually acute, and should decrease over a few days. However, pain can become chronic and persist as a result of disease progression or inadequate control of early nociceptor or nerve discharge.

Pharmacological pain management

Analgesics act at many different sites. Medicines that mimic endorphins or enkephalins are often used to treat pain. Drugs that release, mimic or potentiate the effects of GABA also have analgesic activity, and are used for chronic pain or where there is nerve damage.

Some drugs (eg, non-steroidal anti-inflammatory drugs) act at the site of injury, decreasing the pain associated with inflammation, whereas others alter nerve conduction (eg, local anaesthetics, antiepileptic drugs). Opioids, sedatives and antidepressants modify

Panel 1: Modulation of nociceptive impulses

The transmission of information from peripheral afferents to secondary neurones in the central nervous system is subject to a mechanism that modulates pain perception, often referred to as "gate control theory". Devised by Wall and Melzack in 1965, the theory states that pain perception is a balance between noxious impulses travelling into the spinal cord and inhibitory impulses within the spinal cord.

Inhibitory interneurons can be activated either by touch or vibration receptor signals from the periphery which travel into the spinal cord through other nerve fibres or by descending impulses from the brainstem and thalamus. This is why rubbing a painful area can relieve pain.

Descending pathways "close" the gate by releasing endogenous opiates or other chemical neurotransmitters. This suggests a mechanism of action for the analgesic action of distraction techniques, trans-electrical nerve stimulation and relaxation.

Endogenous opiates include endorphins, enkephalins and dynorphins

transmission in the dorsal horn or affect the emotional aspects of pain.

Analgesics are generally available in a wide range of formulations and are administered singly or in combination via several routes to achieve adequate pain control. Drugs used can be grouped as simple analgesics (eg, paracetamol), NSAIDs, opioids and adjuvants (eg, antiepileptics, antidepressants). The cause of pain must also be considered when selecting treatment. For example, pain due to muscle spasm can require an antispasmodic or muscle relaxant and nerve compression or damage would benefit from dexamethasone or antiepileptic drugs. Bone pain is best treated with NSAIDs and pain from small superficial wounds with a local anaesthetic.

The World Health Organization's "analgesic ladder" (see Panel 2) can be applied to acute pain, such as post-operative pain.

Pain intensity depends on the type of surgery. Numerous studies have assessed analgesics (alone or in combination) for a wide range of surgical procedures. However, it is difficult to correlate pain intensity and surgery type, due to wide interpatient variation.

The Oxford league table of analgesic efficacy shows each drug in terms of numbers of patients who need to be treated to achieve a 50 per cent reduction in moderate or severe pain, in comparison with patients given a placebo over a four- to six-hour period in double-blind single-dose studies. No consideration is given to side effect profiles or drug cost.

Non-opioid analgesics Non-opioid analgesics are used as step 1 pain relief or as adjuvants.

Paracetamol Paracetamol is useful in providing background analgesia alongside other analgesic drugs. The exact mechanism of action for paracetamol is unclear, but its analgesic action is thought to be due to inhibition of prostaglandin synthesis. Its antipyretic property can be of added benefit. An intravenous formulation has recently been licensed in the UK for short term treatment of moderate pain, including after surgery.

NSAIDs NSAIDs inhibit the enzyme cyclooxygenase and, therefore, the production of prostaglandins, prostacyclin and thromboxanes. Conventional NSAIDs (eg, ibuprofen, diclofenac and indomethacin) inhibit both COX-1 and COX-2 isoenzymes. COX-1 is involved in the synthesis of protective prostaglandins (eg, in the gastric mucosa, kidneys and on platelets), while COX-2 is predominantly involved in the inflammatory response.

The inhibition of prostaglandins PGE2 and PGI2 leads to gastrointestinal side effects and renal impairment because these prostaglandins act as gastroprotectants by inhibiting acid secretion and as vasodilators in the kidneys. Inhibition can reduce renal blood flow and precipitate acute renal failure. Prolonged NSAID use can result in intersti-

tial nephritis and chronic renal failure. COX-2-selective NSAIDs (eg, meloxicam, celecoxib, paracetamol and valdecoxib) should be less damaging to the gastrointestinal tract and renal function and have less effect on platelet function.

However, recent safety concerns have led to the discontinuation of rofecoxib and COX-2-selective NSAIDs are now best avoided in patients with cardiovascular risks. NSAIDs are often used in combination with opioids in order to minimise the dose-related side effects of both drug groups. They are available in a wide range of formulations. NSAIDs are occasionally administered concomitantly with H₂ antagonists or proton-pump inhibitors for a gastro-protectant effect in the peri-operative period.

Opioids The term "opioid" is applied to any substance that produces morphine-like effects. Morphine analogues can be classified into:

- Pure agonists (mainly have strong agonist activity at one receptor site only, and possible weak agonist activity at one or more other receptors)
- Weak agonists (weak agonist activity at one receptor site)
- Partial agonists or mixed agonist-antagonists (agonist activity at one receptor site and antagonist effect at another)
- Pure antagonists (antagonist activity at one or more receptor sites)

Synthetic derivatives with structures unrelated to morphine but with similar pharmacological effect include:

- The phenylpiperidine series (eg, pethidine and fentanyl)
- The methadone series (eg, methadone and dextropropoxyphene)
- The benzomorphan series (eg, pentazocine)
- The thebaine derivatives (eg, buprenorphine)

Opioids mainly differ in terms of their receptor specificity and efficacy. There are three principal receptor types: μ , κ and δ and drugs can be classified based on their differing receptor specificity and efficacies.

Pure agonists (typical morphine-like drugs) have a high affinity for μ receptors and varying affinity for δ and κ receptors. Codeine, methadone and dextropropoxyphene are also agonists but with a lesser action at the μ receptor and so are referred to as weak agonists. Partial agonist and mixed agonist-antagonists include buprenorphine and pentazocine.

Opioids are thought to mimic the action of the endogenous pain killing peptides, endorphins, dynorphins and enkephalins. They work best for dull pain (mediated by C fibres) and are not as effective for sharp pain. If comparisons are to be made between opioids in terms of potency or adverse effect profile,



In post-operative pain, analgesia may be started at a higher rung and stepped down

Psychological or physical dependence and withdrawal symptoms are not common when opioids are used appropriately for short term relief of acute post-operative pain

Panel 2: Analgesic ladder

The World Health Organization's analgesic ladder is a three-step approach to pain relief. The idea is to move to the next step if a previous step proves ineffective. Step 1 involves use of simple non-opioid analgesia. Step 2 uses weak opioids and step 3 uses strong opioids. Post-operative pain, however, starts at its peak intensity and improves over time, so analgesia may be started at a higher rung and stepped down as pain improves. Adjuvant therapy (eg, NSAIDs or tricyclic antidepressants) can be used at all three levels. Pre-emptive analgesia attempts to prevent the perception of pain and the neurophysiological and biochemical consequences of a noxious input to the central nervous system.

equi-analgesic doses of drugs should be compared.

All opioids can produce psychological or physical dependence and withdrawal symptoms can occur on sudden discontinuation. These effects are not seen when opioids are used appropriately for short term (a few days) relief of acute post-operative pain. All opioids, weak or strong, can induce side effects, such as constipation, nausea (adding to the nausea that pain can cause) and vomiting. Patients can develop tolerance to nausea and vomiting but tolerance to constipation is less common.

Weak opioids About 10 per cent of the weak μ agonist codeine (3-methyl morphine) is metabolised to morphine (via demethylation). Unlike morphine, it causes little euphoria and is only one twelfth as potent as oral morphine. Dihydrocodeine is a synthetic derivative of codeine. It is slightly more potent (one 10th the potency of oral morphine) but has no substantial advantage over codeine (the side effect profile is similar). Tramadol is a synthetic opioid that also acts centrally. It is thought to have fewer opiate side effects, but is associated with hallucinations and seizures and should, therefore, be avoided in patients with a history of epilepsy. Tramadol has one 10th the potency of oral morphine.

Strong opioids Morphine is a pure opioid receptor agonist. It mainly acts at μ receptors, but has some action at κ and δ receptors. It is the standard against which the potency of other opioid analgesics is measured. Quick release oral preparations of morphine include Oramorph and Sevedol. Slow release preparations include MST (twice daily) and MXL (once daily). However, for post-operative pain, morphine is initially given parenterally. It can be administered subcutaneously, intravenously, intramuscularly, intrathecally or epidurally but the iv route is preferred for rapid onset of action, more predictable blood levels and ease of administration.

Oral morphine has poor bioavailability due to extensive first-pass metabolism in the liver. Subcutaneous or intravenous morphine is, therefore, twice as potent as oral morphine.

One of the metabolites of morphine (morphine-6-glucuronide) has analgesic properties in its own right. Another metabolite (morphine-3-glucuronide) is thought to antagonise the analgesic action of morphine and is thought to be responsible for paradoxical pain occasionally seen in some patients, despite an adequate dose of morphine.

Diamorphine, a diethyl derivative of morphine, has a higher lipid solubility than morphine, but also retains a high water solubility, allowing it to be prepared and administered in small volumes. Subcutaneous diamorphine is three times as potent as oral morphine. Its duration of action is shorter than that of morphine.

Oxycodone is twice as potent as morphine. It has fewer hallucinogenic effects, and is commonly used in patients who have intolerable side effects to morphine.

Pethidine is a synthetic opioid with a shorter duration of action than morphine. It produces similar euphoric effect. One of its metabolites, norpethidine, can accumulate (especially in renal impairment) and cause hallucinations and convulsions. Pethidine may interact with peri-operative drugs, for example, with monoamine oxidase inhibitors it can cause severe excitation or depression of the central nervous system, or hypertension or hypotension. It may also antagonise the effect of metoclopramide and domperidone on gastrointestinal activity.

Fentanyl is a synthetic opioid related to pethidine. It is highly potent, with similar effects to morphine but a shorter duration of action. It also has a higher lipid solubility and can be administered transdermally, intravenously or as a preparation for buccal absorption (Actiq lozenges). Fentanyl, alfentanil and remifentanyl are suitable alternatives to morphine where a rapid but short duration of action is desired.

Methadone has good oral bioavailability and a half life of over 24 hours. It is not used for managing post-operative pain but may be used in the peri-operative period to avoid withdrawal effects in patients who are dependent on heroin or methadone. It may accumulate in patients with renal impairment.

Partial opioid receptor antagonists, such as buprenorphine and pentazocine, only produce partial stimulation of opioid receptors. They exhibit less sedation and respiratory depression than morphine but also have a "ceiling effect" to their analgesic properties and may not relieve severe pain. If they are administered concomitantly with another full agonist, they can reduce the effect of the true agonist. Buprenorphine is a semi-synthetic derivative of thebaine, which has intermediate effectiveness between codeine and morphine. It is highly lipid soluble, and acts as a partial agonist at μ receptors. It is administered sublingually. Buprenorphine (a partial agonist at μ and antagonist at κ receptors) is less likely to cause dysphoria than pentazocine, but is more likely to cause respiratory depression, which may not be fully reversible with naloxone.

Pentazocine is a partial agonist at δ and κ receptors and antagonist at μ receptors. At low doses, pentazocine has a potency similar to



Other interventions for managing pain include acupuncture

morphine but quickly reaches its ceiling analgesic effect.

Naloxone Naloxone is a pure opioid antagonist at μ , δ and κ receptors. Peri-operatively, it is used to reverse respiratory depression caused by excessive opioid administration. It is administered intravenously and produces an immediate action. However, its duration of action is relatively short (1-2 hours) due to its rapid metabolism in the liver. Re-sedation and respiratory depression can, therefore, occur if naloxone is metabolised more rapidly than the opioid that was administered.

NMDA receptor antagonists Repeated afferent impulses from the same body area can sensitise the peripheral and central nervous systems and either increase post-operative pain or contribute to the development of chronic pain syndromes. N-methyl-D-aspartate (NMDA) receptor antagonist, such as ketamine, have no effect on the nociceptive input, but reduce the injury induced hyperexcitability of the spinal cord and the subsequent hyperalgesia.

Other interventions Acupuncture, physiotherapy and complementary therapies (eg, massage, aromatherapy, reflexology) are increasingly recognised as helpful in managing pain and many hospitals offer complementary therapies alongside pharmacological pain management. Trans-electrical nerve stimulators are also used as an adjunct to analgesia.

The next article in this series will discuss patient-controlled intravenous and epidural analgesia, nerve blocks and monitoring parameters.

Resources

- For a full description of the physiology of pain, see McMahon S, Koltzenburg M. Wall and Melzack's textbook of pain. 5th edition London: Churchill-Livingstone; 2005.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Investigate the policy your hospital adopts for managing post-operative pain
2. Find out what agents are used to manage opioid side effects (eg, constipation) in your trust.
3. Discuss the use of complementary therapies in post-operative pain with your peers.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)

What will you do now and how will this be achieved?

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