Chapter

Analgesics

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Abstract

It is the responsibility of the professional care team to develop an effective person-centred Pain Management strategy which appropriately assesses patients, analyses the results of the assessment and devises a person centred plan to manage pain while allowing the person to remain as independent and functional as possible. The medications useful in treating acute pain are similar to those used in treating other types of pain. The World Health Organization (WHO) analgesic ladder developed for treating patients with cancer pain also provides a useful approach to treat acute pain. At the lowest level (mild pain) are recommended nonopioid analgesics such as paracetamol or/plus nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprophen). Such drugs have an analgesic ceiling; above a certain dose, no further analgesia is expected. For moderate pain, are recommended combining paracetamol and/or a NSAID with an opioid (a weak opoid). The inclusion of paracetamol limits the amount of opoids that should be used within 24 hour period, with many benefits which will be discussed later in the chapter. For severe level of pain, a strong opoid such as morphine is a better choice; such opoids have no analgesic ceiling. Most postoperative or trauma patients initially respond better to a morphine-equivalent opoid. At the moment when the patient is eating and drinking, a combination of oral analgesics including opoids and paracetamol plus/minus NSAID are most of the time an adequate choice.

Keywords: pharmacology, pharmacokinetics, doses, effects, interactions, side effects

1. Introduction

Pain is inevitable, suffering is optional.

(Dalai Lama)

Pain-related complaints represent as many as 70% of presenting concerns for patients in the A&E departments or GP setting [1–3]. A wide variety of options are available for the treatment of pain, from which the most known and used are the analgesics.

The approach to patients in pain should use a division of pain patients into four specific treatment groups: acute pain, chronic pain, recurrent pain and chronic pain of malignancy. In this chapter we will address mostly to the acute pain management.

Pain treatment should be initiated promptly, titrated to an acceptable level of relief, and continued during the cause's investigation. It is inappropriate to delay analgesics use until a diagnosis has been made. There is no evidence that the administration of adequate doses of opioid analgesia to establish patient comfort impairs the medical ability to rich a diagnose of an emergency condition. To the contrary,

administration of analgesia may enhance the accuracy of physical examination and patient assessment [4, 5].

The medications useful in treating acute pain are similar to those used in treating other types of pain [1]. The World Health Organisation (WHO) analgesic ladder (**Figure 1**) developed for treating patients with cancer pain also provides a useful approach to treat acute pain. At the lowest level (mild pain) are recommended nonopioid analgesics such as paracetamol or/plus nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprofen). Such drugs have an analgesic ceiling; above a certain dose, no further analgesia effect is expected [1]. For moderate pain, are recommended combining paracetamol and/or a NSAID with an opioid (a weak opioid). The inclusion of paracetamol limits the amount of opioids that should be used within 24 hour period, with many benefits which will be discussed later in the chapter. For severe level of pain, a strong opioid such as morphine is a better choice; such opioids have no analgesic ceiling. Most postoperative or trauma patients initially respond better to a morphine-equivalent opioid. By the moment the patient is eating, drinking and ready for discharge, a combination of oral analgesics including opioids and paracetamol plus/minus NSAID are most of the time an adequate option.

Not all types of pain respond equally to the same medication. Usually NSAIDs and steroids are highly effective in controlling soft tissue and bone pain. Bone pain may be helped partially by opioids [1]. But overall, the combination of NSAIDs, paracetamol and opioids is synergistic in treating the most types of pain. Opioid analgesics are useful in controlling somatic and visceral pain. Neuropathic pain, often described as pain with a burning and hyperaesthesia characteristic, which responds well to a diverse group of drugs, called adjuvants, including low dose of antidepressants (amitriptyline), anticonvulsants (carbamazepine and clonazepam), antiarrhythmics (mexiletine), baclofen and alfa-adrenergic agonists (clonidine). Opioids may also be helpful [1]. Most of the time, analgesia is improved after 1–2 days of using adjuvant drugs. Adjuvants were not developed initially as analgesics but recent studies show they poses benefits in a better pain control. Drugs that control pain by different mechanisms of action may be synergistic, when used together. Also, by lower doses of two or more different agents, the patient may have better pain control with fewer side effects. This is the basic background for the multimodal analgesia concept.

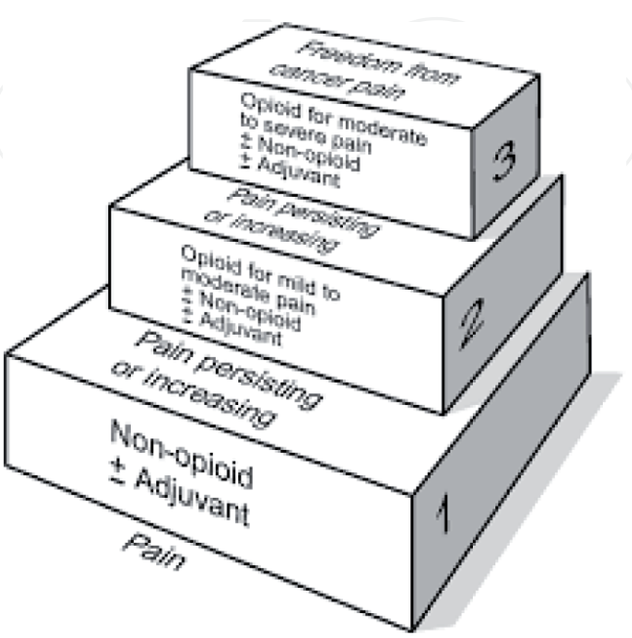

Figure 1.
WHO analgesic ladder.

2. Nonopioid analgesic agents

2.1 Paracetamol

Paracetamol is the first-line agent for the treatment of both acute and chronic pain. It is one of the pain killers with the highest profile of safety and is a first pharmacologic option for controlling pain in children and adults. It has a high toxic-to-therapeutic ratio and has very few significant drug interactions compared with other analgesics [2].

It can be given orally, rectally or parentally, has small anti-inflammatory activity, and is an effective analgesic and antipyretic.

Although paracetamol has been in use since 1880, its pharmacologic mechanism of action is not fully known. It has a rapid absorption from the small intestine after oral administration. Paracetamol has lower protein binding than NSAIDs (and hence fewer potential drug interactions) and higher volume of distribution [6].

Paracetamol is the active metabolite of the earlier (more toxic) drugs acetanilide and phenacetin. The recommended dose in adults is 0.5–1 g oral, iv or rectal every 4–6 hours when necessary, without exceeding a total daily dose of 4 g [6].

Paracetamol has a CNS action, where inhibits prostaglandin synthesis. In clinical doses it has insignificant peripheral anti-inflammatory action. Unlike morphine, paracetamol has no apparent biding sites, and unlike NSAIDs it does not inhibit peripheral cyclo-oxygenase activity. But however, his mechanisms of action include, beside central COX-2 inhibition [2, 7], inhibition of a central cyclo-oxygenase, COX-3, that is selectively susceptible to paracetamol, and modulation of descending serotonergic pathways that suppresses spinal cord nociceptive transmission. There is also evidence of agonism at the cannabinoid receptor CB_1 [2, 8]. There are, other evidences that paracetamol may inhibit prostaglandin endoperoxidase H_2 production at the cellular level, independent of cyclooxygenase activity [2, 6].

The most recent Cochrane review [9] of RCTs of single-dose oral analgesic for acute postoperative pain in adults reported a NNT of 3·6 with 1 g paracetamol, when morphine 10 mg IM has 2.9, ibuprofen 400 mg - 2.4 and codeine 60 mg - 16.7. Efficiency of paracetamol is improved in combinations with other analgesics, such as 400 mg ibuprofen, 60 mg codeine and 10 mg oxycodone (NNT 1·5, 2·2 and 1·8 respectively) [6, 9].

So, paracetamol is an effective analgesic, with potency somewhat less than standard dose of morphine. Paracetamol is an efficient adjunct to opioid analgesia, and regular administration after surgery produce an opioid sparing effect, because reduce opioid requirements by 20–30%. Paracetamol proved to be an integral component of multimodal analgesia in combination with NSAIDs and opioids. Paracetamol has less side effects than the NSAIDs and can be used when the latter are contraindicated.

A significant concern regarding paracetamol use relates to the development of hepatotoxicity; however, current data suggest this is unlikely to develop at therapeutic doses [10]. However, doses of more than 150 mg/kg of paracetamol taken within 24 hours may result in severe liver damage, hypoglycaemia and acute tubular necrosis, especially when associated with dehydration and chronic malnutrition [11]. Individuals taking enzyme-inducing agents are more susceptible. So, important caution should be taken in overdoses due to the risk of liver damage and less frequently renal damage. Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of a right-side subcostal pain and tenderness, usually indicates development of hepatic necrosis.

Side effects	Rare	Frequency not known
General	Acute generalised exanthematous pustulosis Malaise Skin reactions • Steven-Johnson syndrome • Toxic epidermal necrolysis	Blood disorders: leucopoenia neutropenia, thrombocytopenia as is bone marrow suppression
Specific	With iv use, flushing and tachycardia	With iv use, hypotension

Table 1.
Paracetamol side effects.

Paracetamol is metabolised in the liver primarily through conjugation to sulphate or glucuronides [2]. A minor pathway for the oxidative metabolism of paracetamol produces the toxic metabolite N-acetyl-P-benzoquinone (NAPQI) [2]. NAPQI requires glutathione for detoxification and elimination. Hepatic toxicity can occur when glutathione pathways are overwhelmed by an increase in NAPQI or decrease in glutathione.

Paracetamol is generally well tolerated with rare side effects when the right doses are prescribed (**Table 1**) [2, 4].

2.2 Interactions

It is associated with several important drug interactions. Many anticonvulsants, including phenytoin, barbiturates and carbamazepine induces hepatic microsomal enzymes. Increased conversion of paracetamol to its toxic metabolite may occur in patients who are taking anticonvulsants, but this rarely leads to concerning consequences in the context of the usual doses for pain management [2, 6].

Although uncommon, drug interaction resulting in an increased INR is reported for patients taking both paracetamol and warfarin, particularly among patients taking high doses of paracetamol (> 9 g/week) [2, 12, 13]. Long term use of paracetamol should be avoided in patients with hepatic or renal impairment. Patients with a history of salicylate hypersensitivity characterised by urticaria have a 11% cross-reactivity to paracetamol, and the agent should be used with caution in this group [2, 7].

3. Nonsteroidal anti-inflammatory drugs

The NSAIDs share several properties with aspirin and may be considered together.

NSAIDs are particularly used for the treatment of patients with chronic disease accompanied by pain and inflammation.

Some of them are also used for acute pain management and in the short-term treatment of mild to moderate pain including transient musculoskeletal pain. They are also suitable for the pain control in dysmenorrhoea and to release pain caused by secondary bone tumours, many of which produce lysis of bone and increase prostaglandins synthesis. Many of the NSAIDs are also used for postoperative analgesia as part of the multimodal analgesia strategy. Selective inhibitors of COX2 may be used in preference to non-selective NSAIDs for patients at high risk of developing serious gastro-intestinal side-effects.

There are some limited and low quality evidences against the use of NSAIDs in bone pathology, suggesting that prostaglandins promote bone formation and that NSAID might impair this process [14, 15], theory not proven through properly

conducted studies. There is no evidence that NSAIDs administration on short term after fracture is detrimental to healing [2].

3.1 Mechanism of action

3.1.1 Prostaglandin synthesis inhibition

These agents inhibit cyclooxygenase (COX) and, as result, the synthesis of prostaglandin, a key mediator of inflammation, in the peripheral tissues, CNS and nerves – leading to an effective raise in the threshold of nociceptors stimulation. Aspirin acetylates and irreversibly inhibits cyclo-oxygenase, while NSAIDs work by competitive inhibition, being reversible. The prostaglandins are part of the eicosanoid's family, oxygenated metabolites of arachidonic acid and other polyunsaturated fatty acids that include leukotrienes [6].

The rate of prostaglandin synthesis is usually low, being regulated by trauma and tissue stimuli, which activates phospholipases to free arachidonic acid, from which prostaglandins are produced. Prostaglandins have several physiological roles, including gastric mucosal protection, bronchodilation and maintenance of renal tubular function, renal vasodilatation, regulation of tubular electrolytes and modulation the action of renal hormones [2, 6]. The side effects on the renal system of chronic NSAIDs is well known. In certain clinical settings when there are high plasma concentration of the vasoconstrictors rennin, noradrenaline, angiotensin and vasopressin, intrarenal vasodilators including prostacyclin are produced and renal function can be affected by NSAIDs administration [2]. The concomitant use of other potential nephrotoxic drugs, such as gentamicin, can worsen the renal effect of these drugs [2]. Nevertheless, with careful patient selection and closed monitoring the incidence of NSAID-renal damage is low.

Triggering bronchospasm is a recognised phenomenon in patients with asthma, rhinitis and nasal polyps [2]. Such "aspirin induce asthma" can be severe, and goes up to 10–15% as incidence with a feature cross sensitivity with NSAIDs. A known history of aspirin induce asthma should band the administration of NSAIDs perioperatively. The mechanism is unclear, but practice shown the reaction increases with the potency of the COX inhibition [2].

Endothelial released prostacyclin induces vasodilatation and prevents platelet adhesion, and platelet thromboxane produces aggregation and vasospasm. In addition to prostaglandins, cyclooxygenase induces prostacyclin synthesis, a vasodilator that also increases GI mucosal perfusion. Also, in the gastric tissue, COX-1 increases mucus and bicarbonate production, valuable feature for stomach mucosal protection [2]. Inhibition of COX-1 is affecting this protection, predisposing to ulcerations and bleeding, which can be exacerbated by concomitant NSAID-induced platelet dysfunction [2].

3.1.2 Cyclo-oxygenase isoenzymes

Two subtypes of cyclo-oxygenase enzyme have been identified. These are constitutional COX-1 and inducible COX-2, the last one triggered by inflammation and trauma. The COX-1 is present in all cells and regulates various roles in homeostatic function. NSAIDs, like aspirin, are non-selective cyclo-oxygenase inhibitors that act on both COX-1 and COX-2, which results in multiple beneficial effects (reduction in inflammation, pain and fever) but also some important side effects.

These two COX isoenzymes have 75% aminoacid homology, with almost identical enzymes kinetics.

COX-1 is a membrane bound haemoglycoprotein found in the endoplasmic reticulum of prostaglandin-inducing cells. The COX active site is a long hydrophobic

channel. NSAIDs block COX-1 halfway down the channel by hydrogen bounding in a reversible fashion. Aspirin acetylates serine, irreversibly preventing access for arachidonic acid [6].

COX-2 has similar sites to COX-1 for the attachment of arachidonic acid, and a similar three-dimensional structure to COX-1.

Under physiological condition COX-1 activity predominates, to produce prostaglandins that regulate rapid physiological responses such as vascular homeostasis, gastric function, platelet activity and renal function. The concentration of the COX-1 isoenzyme is low, but it may increase 2 to 4-fold, triggered by grow hormones and various hormones stimulation. Low concentration of COX-2 can normally be detected in the brain, kidney and the pregnant uterus. COX-2 mRNA expression by synovial cells, fibroblasts, monocytes may be increased 10 to 80-fold when stimulated by cytokines, bacterial lipopolysaccharides or growth factors [6] These triggers increase COX-2 synthesis and tissue PGE2 concentration, resulting in inflammation and pain.

Inhibition of COX-1 induces antiplatelet activity that might be cardioprotective by inhibition of thromboxane synthesis more than prostacyclin. Inhibition of COX-2 inhibits prostacyclin synthesis more than thromboxane and may induce prothrombotic effects, leading to a higher risk of cardiovascular events [2]. In the case of nonselective COX inhibitors, both effects appear to be in balance each other out, resulting in minimal changes in cardiovascular risk [2]. But instead, the action of COX-2 inhibitors may result in result in an increased cardiovascular risk [16, 17].

Prostaglandins released by COX-1 is also a factor on keeping a good glomerular filtration rate (GFR) by renal vasodilatation that maintain renal blood flow. Inhibition of COX-1, especially in dehydrated patients can lead to affect GFR and even to an acute kidney injury [2]. Other condition that might worsen under NSAIDs treatment is congestive heart failure, due to sodium and water retention, hyperkalaemia, hypertension and acute renal failure.

The most common adverse effect of NSAIDs is GI mucosal erosion. In patients taking chronic NSAIDs (continuously for 1 year) 10 to 60% will experience abdominal pain, nausea, dyspepsia, and a 2 to 4% will end up with a symptomatic peptic ulcers [18]. Between the risk factors are known: age, concomitant use of corticosteroids and warfarin, coronary artery disease, congestive heart failure and diabetes mellitus. Several studies proved the efficiency of some protective agents as misoprostol and proton pump inhibitors [19]. The relative risk for causing GI effects under the NSAIDs treatment are shown in **Table 2** on below.

3.2 Side effects

This category of drugs is widely used, being very efficient medicines, but responsible for more serious drugs-related side effects than any other class of analgesic drugs [20]. The main side effect of NSAIDs as stated earlier is gastric erosion with the risk of GI bleeding, but also platelets dysfunction, renal failure and anaphylaxis or bronchospasm in individuals who have “aspirin – induced asthma” [2].

Single dose of NSAIDs such as diclofenac and ketorolac inhibit platelet function (prolong skin bleeding time and inhibit platelet function in vitro), but do not tend to increase bleeding in normal patients. However, when concomitant anticoagulation treatment or presence of subclinical bleeding diathesis occurs, then there is an increased risk of surgical bleeding [2].

Conversely, NSAIDs and COX-2 inhibitors have a small prothrombotic tendency. The risk is increasing by prolonged administration and by the dose taken, and for the more selective agents (COX-2) but also for diclofenac [2]. Studies shows that diclofenac 150 mg has similar risk to etoricoxib. Ibuprofen in a daily dose of 2400 mg also

NSAID	*Relative risk of serious GI toxicity*
COX-2 inhibitor	0.6
Ibuprofen	1.0
Diclofenac	1.8
Naproxen	2.2
Indomethacin	2.4
Piroxicam	3.8
Ketoprofen	4.2
Ketorolac	24.7
Risk reduction when added to ibuprofen	Proton pump inhibitor
0.09	Misoprostol
0.57	

Table 2.
Risk of serious gastrointestinal effects of NSAIDs [18, 19].

represents a high risk for thrombosis. But reduced doses to 1200 mg a day Ibuprofen and Naproxen 1 g daily are not associated with an increase risk [21, 22].

3.3 Contraindications of NSAIDs

There are many contraindications of this drug class presented on below (**Table 3**) [23].

3.4 Efficiency of the NSAIDs

The number needed to treat (NNT, basically the number of patients in a study to whom the drug must be given to show a benefit) for diclofenac 50 mg 2.3, ketorolac 10 mg is 2.6 and ibuprofen 400 mg 2.4. For comparison, the NNT of morphine 10 mg

Relative contraindications	**Absolute contraindication**
Impaired hepatic function, diabetes, bleeding or coagulation disorder, vascular disease	History of GI bleeding or ulceration
Surgery with a high risk of intraoperative haemorrhage (cardiac, vascular, etc.)	Known allergy to NSAIDs
Surgery where an absence of bleeding is important (eye surgery or neurosurgery)	Sever liver dysfunction
	Cardiac failure (risk of sodium, potassium and water retention)
Concurrent use of ACE inhibitors, potassium sparing diuretics, anticoagulants, methotrexate, cyclosporin, gentamicin	Dehydration, hypovolemia, hypotension
Pregnant and lactating women	Hyperkalaemia
Age >65 years (risk of kidney impairment)	Pre-existing renal impairment
Uncontrolled hypertension	
Aspirin-induced asthma	

Table 3.
NSAIDs contraindications.

IM is 2.9 and codeine 60 mg PO is 16.7. When given in combination with opioids, NSAIDs optimise the pain control and decrease opioid consumption by 25–50% [2]. NSAIDs are insufficient as a single pain killer use for relief of very severe pain.

COX-2 inhibitors produce less clinically significant peptic ulceration than other NSAIDs. So, COX-2 inhibitors are not far from any incidence of this adverse event, and there still debates on COX-2 inhibitors use in patients who have various risk factors for gastric erosion.

Platelets do not produce COX-2 (only COX-1) and so, COX-2 selective inhibitors do not affect platelet function. Studies have proved the lack of and antiplatelet effect of COX-2 inhibitors, and a reduction in surgical bleeding in comparison to other NSAIDs.

COX-2 is resident (constitutive) in some tissues including the renal, and COX-2 inhibitors have similar adverse effects on renal function to the non-selective NSAIDs (**Table 4**) [2].

3.5 Drug interactions

Aspirin. NSAIDs may impair the cardioprotective feature of aspirin, but this subject is still debatable lacking of strong evidences against use of NSAIDs for acute pain or inflammation in a patient on chronic daily aspirin use [24, 25].

Oral Anticoagulants. NSAIDs have an antiplatelet effect, added to the anticoagulant properties of warfarin, is exponential increasing the risk of significant bleeding complications, especially from the GI ulcers. Furthermore, NSAIDs displace protein-bound warfarin and is leading to increase the prothrombin times during a constant warfarin dose [18]. NSAIDs should be avoided in patients who are taking warfarin.

ACE Inhibitors. Concomitant use of NSAIDs with ACE inhibitors may impair kidney function and may prejudice the antihypertensive effect of ACE inhibitors.

Diuretics. Patients on diuretics have a higher risk of developing renal failure because of NSAIDs-mediated decreased kidney blood perfusion. Also, the natriuretic response to diuretics is in relation with prostaglandin-mediated vasodilatation.

Glucocorticoids. Patients on corticosteroids possess a higher risk of peptic ulcer. NSAIDs should be avoided in patients concomitantly taking corticosteroids unless closely supervised.

	NSAIDs	**COX-2**
Efficacy for moderate to severe acute pain (numbers to treat – NNT)	Diclofenac 50 mg (2.3) Ibuprofen 400 mg (2.4) Ketorolac 10 mg (2.6)	Celecoxib 200 mg (4.5) Parecoxib 20 mg (3.0) Etoricoxib 120 mg (1.8)
Renal function	Can impair renal function postoperatively	Similar adverse effects
Gastrointestinal	Acute gastrointestinal damage and bleeding can occur. Risk increased with higher doses, history of GI ulceration, long term use, and elderly	Less clinically significant peptic ulceration
Platelet function	Inhibit platelet function but do not significantly increase surgical blood loss in normal patients. Associated with higher incidence of post-tonsillectomy bleeding	Do not impair platelet function
Aspirin-exacerbated respiratory disease	10–15% of asthmatics affected when given aspirin. Cross-sensitivity with NSAIDs	Do not produces bronchospasm
Bone healing	Impaired in animal studies. No strong evidences that clinically important	Similar to NSAIDs

Table 4.
Comparison of non-selective NSAIDs and COX-2 inhibitors.

Lithium. NSAIDs increase lithium reabsorption and may reduce lithium excretion, and cause subsequently increases lithium levels. CNS manifestations (confusion, drowsiness, vertigo, tremors, seizures), QRS complex widening and cardiac arrhythmias are warning signs of lithium toxicity. The lithium doses should be reduced in patient concurrently taking NSAIDs.

Methotrexate. Chronic use of NSAIDs and methotrexate have resulted in prolonged, increased levels of methotrexate, leading to severe toxicity. A possible mechanism is accountable due to decreased renal blood supply, slowing down the elimination of methotrexate.

4. Opioid analgesic agents

In 1680, Sydenham wrote "Among the remedies it has pleased Almighty God to give to man to relive his suffering, none is so universal and so efficacious as opium" [2, 26]. Hundreds of years later, this statement is still valid, and opioids are the cornerstone of pain management. The beneficial effects have been well studied for centuries, as their toxicity and also the potential for abuse.

Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause dependence and tolerance, but this is not deterrent in the pain control of terminal illness. Regular use of a potent opioid may be appropriate for certain cases of chronic non-malignant pain; treatment should be supervised by medical staff and the patient should be assessed regularly. However, due to concerns about inducing opioid toxicity or addiction and sometimes due to poor understanding of the pharmacology features of these drugs, opioids are often inadequate used in clinical practice [27, 28].

4.1 Mechanism of action and toxic effects

Opioids bind to specific endorphin system receptors located throughout the nervous system but not only. Opioid receptors are G-protein-coupled transmembrane receptors. These exist throughout the CNS, with particularly high concentration in thalamus and spinal cord. They are also present outside the CNS, and these are responsible for other opioids effects (gastrointestinal tract) and their postulated value in some peripheral anaesthetic techniques, such as intra-articular infiltrations [6]. The actions of various opioids are induced by the specific binding properties of the agent to the various receptors (**Table 5**).

Opioid receptor class	Effects	Associated endogenous endorphin
Miu 1	Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential	Beta-endorphin
Miu 2	Respiratory depression, CV and GI effects, miosis, urinary retention	Beta-endorphin
Delta	Spinal analgesia, CV depressions, decreased brain and myocardial activity, physical dependence	Enkephalin
Kappa	Spinal analgesia, dysphoria, psychotomimetic effects, feedback inhibition of the endorphin system	Dynorphin, Beta-endorphin
Epsilon	Hormone	Beta-endorphin
Gamma	Dysphoria, psychotomimetic effects	Beta-endorphin

Table 5.
Opioids receptors end their effects.

Opioids decrease the medullary sensitivity to CO_2, which may cause respiratory depression and also, suppress the medullary cough centre, for this reason some studies advocate for its use as an antitussive. Opioids can activate the chemoreceptor trigger zone, causing nausea or vomiting, but this is relatively infrequent. This drug class decrease bowel motility and smooth muscle function, responsible for constipation, and rarely, urinary retention. To a varying degree, some opioids destabilise mast cells in a dose dependent fashion, causing histamine release, manifested with pruritus, urticaria and sometimes, orthostatic hypotension.

4.2 Clinical effect

Opioid agonist agents cause a range of mainly depressant and some stimulant actions of the CNS through specific receptors (**Table 6**). These drugs have little capacity to produce amnesia, do not alter seizure threshold and have no anticonvulsant activity [6].

Opioids given systemically produce analgesia through actions at two anatomically distinct regions: supraspinal and spinal sites. They efficiently reduce the intensity of pain and the associated fear. This is achieved by raising the pain threshold, modifying the reaction to pain, and inducing sleep. They are efficient for controlling dull pain rather than sharp intermittent pain. Opioids are less effective for the treatment of neuropathic pain.

Opioids actions are also towards reduction in the level of consciousness and eventually produce sleep, with the loss of responsiveness to verbal stimulation. In anaesthesia combinations, they produce a dose related decrease in the MAC for volatile anaesthetics, with a ceiling of 60–70% decrease in MAC [6]. Another important feature in the combination with the volatile agents is increase in cerebral vasoconstriction [6]. Opioids do not cause a loss of cerebral autoregulation or reactivity to CO_2. During EEC recording, there is a ceiling effect, with a slowing EEG frequency and the production of high-voltage (delta) waves [6].

4.3 Cardiovascular effects

In normovolemic patients, opioids barely influence haemodynamic parameters, with minimal cardiac depression, no baroreceptors inhibitions and modest reduction in preload and afterload. Haemodynamic compromise may be detected in subjects whose cardiovascular integrity is dependable on a high level of sympathetic tone, because opioids decrease central sympathetic outflow when even small doses can cause hypotension and circulatory collapse [6]. Morphine has the greatest effect on the vascular system. Morphine has the greatest effect on histamine release and subsequent indirect effect on catecholamine release. This may lead to tachycardia with a reduction in systemic vascular resistance (SVR) and mean arterial pressure (MAP). This risk can be prevented by pre-treatment with an antihistaminic drug and volume loading [6].

Opioids induce a negative chronotropic effect through a central vagal stimulation. Pethidine, however, has a homology with atropine and can trigger tachycardia, and it is the only opioid to induce significant direct myocardial depression when used at high doses. Myocardial depression is observed also after extraordinary high doses of morphine and fentanyl, as during cardiovascular anaesthesia. Morphine has indirect positive inotropic effects at doses of 1–2 mg/kg, and blocks neurally and hormonally mediated venoconstriction to reduce preload, rendering it useful in the management of left ventricular failure [6].

Opioids preserve circulatory stability to a greater extent than most other anaesthetic agents [6].

System		Effect
Musculoskeletal	Gait	Decrease physical performance Ataxia Decrease spinal cord reflexes
	Rigidity	Muscular rigidity occurs 60–90 seconds post-injection and abolish after 10–20 minutes Mainly thoracoabdominal and arms muscles, higher risk with advanced age, high speed of injection, increased dose, use of N_2O Mediated via nucleus raphe magnus
	Multifocal myoclonus	Non-convulsive related, higher risk with pethidine
Neural	Central	Spectrum from abnormal eye movement, to contraction of extremities, to tonic-clonic movements Euphoria: especially for opioids which cross the blood-brain barrier quickly Dysphoria in some individuals Subjective feelings of body warmth and heavy extremities Apathy Decreased level of consciousness Decreased concentration and orientation
	EEG	Effects vary between different opioids: slowing of frequency, production of high voltage & waves No capacity to induce EEG silence
Vision	Edinger-Westphal nucleus	Miosis (via a decrease in inhibition to the nucleus) except pethidine Reversed by hypoxia and atropine
Cerebrovascular	SSEPs	No effect
	ICP	No effect
	CBF	No effect, but increased vasoconstriction with vasodilators No loss of autoregulation or CO_2 reactivity $CMRO_2$ reduced by up to 10–25%
Thermoregulation	Response	Decrease thermoregulation response (as for volatile agents)
	Peripheral effects	Promote hypothermia via decreased BMR (10–20%), venodilation, muscle relaxation

SSEPs – somatosensory evoked potential, ICP – intracranial pressure, $CMRO_2$ – cerebral metabolic rate of oxygen consumption.

Table 6.
Opioids effects on the CNS [6].

4.4 Effects on other organ systems

Opioids are the most efficient of all pain analgesics drugs for attenuating the stress response associated with pain, laryngoscopy and airway manipulation. The plasma concentration of stress hormones (cortisol, catecholamines, vasopressin, aldosterone and growth factor) increases during trauma, anaesthesia or surgery. This produce increased myocardial work, tissue catabolism and hyperglycaemia – effects associated with increased morbidity and mortality. Opioids reduce nociception inhibiting the pituitary-adrenal axis, decreasing central sympathetic outflow and influencing centrally mediated neuroendocrine response. Fentanyl and its congeners are the most efficacious in this action (**Table 7**).

System		Effect
Cardiovascular	Heart rate	Sinus bradycardia via central vagal stimulation Occasionally sinus arrest exacerbated by concomitant vagal excitation (e.g. laryngoscopy) and Beta-blockers
	Mean arterial pressure	Usually no effect or a slight decrease (unless significant bradycardia) Greater decrease if associated with histamine release
	Vascular system	No effect on SVR (unless histamine release) Mild venodilation with a decrease in preload (due to decrease of central sympathetic outflow)
	Myocardium	No effect on contractility (except for pethidine which is a depressant) No effect on metabolic rate Possible ischemic preconditioning
	Excitability	Decreased myocardial contractility Increased refractory period Increased VF threshold
Respiratory	Mechanics	Decrease in rate, tidal volume and minute ventilation at equianalgesic doses Increase pauses, irregular breathing and apnoea
	Control	Increased apnoeic threshold Decrease CO_2 sensitivity Decrease carotid body chemoreception and hypoxic drive Voluntary control of respiration remains intact No effect on hypoxic pulmonary vasoconstriction
	Airway reflexes	Decrease airway reflexes with improve tolerance to ETT Antitussive through central and peripheral actions Decrease mucociliary action Brief cough in up to 50% with pethidine bolus
Gastrointestinal	Stomach and bowel	Decrease peristalsis and secretions and increase tone causing dry stool and constipation Decrease gastric acid Decrease gastric emptying with increase antral tone and decrease lower oesophageal sphincter tone promoting high aspiration risk Increase tone of pyloric, ileocecal and anal sphincters
	Biliary tree	Increase bile duct pressure Sphincter Oddi contraction (little clinical significance)
	Chemoreceptor trigger zone	Nausea and vomiting
Genitourinary	Kidney	Antidiuresis as a result of decrease in renal blood flow and decrease in GFR (predominates) Decrease vasopressin release in response to osmotic triggers
	Bladder	Increased bladder and urethral tone Vesicular sphincter contraction
Immunity	Immune system	Decrease immunoglobulin production (uncertain significance) Reactivation of herpes simplex virus 2–5 days after neuraxial opioid

Table 7.
Opioid effects on major organ system [6].

4.5 Side effects

Side effects can be observed from minors to the most concerning ones and are individual and age depending beyond of disease extension, presence of organ

dysfunction, concurrent administration of certain drugs, route of administration and prior of opioid exposure. Some side effects induced by the opioids are induced by the activation of the opioid receptors either peripherally or centrally, or even in both areas. Serious allergic reactions to opioids are extremely rare, although anaphylaxis has been reported.

At equianalgesic doses, all opioids produce equivalent degrees of respiratory depression through reducing the sensitivity to CO_2 of the breathing drive. The extreme ages, elderly and neonates are at the highest risk. Tolerance arises rapidly to this effect, and with chronic opioid exposure the risk of major respiratory depression is reduced. Apnoea may occur in conscious patients, but this is rare, and is usually associated with other signs of CNS depression. In such a condition, apnoeic patients can be instructed to breath as voluntary control of ventilation remains intact. Sleep or the concomitant use of other CNS depressants (except clonidine) potentiates this risk.

Opioid-induce depression of airway reflexes is usually regarded as an advantage side effect for the practitioner in some condition like airway manipulation. Although at the same time the mucociliary function depression can be detrimental. All opioids have an antitussive activity at less than analgesic doses, working via central and peripheral mechanisms.

The incidence of nausea after opioids use is reported to be between 10 and 60%, and this is markedly increased in pain-free and ambulatory patients (via opioid sensitisation of the vestibular nucleus). This reactivity is based on individual variability, but tolerance develops rapidly [6]. Switch to oral administration and substituting one opioid to another may reduce the incidence of nausea.

Constipation remains the most common side effect of chronic opioid treatment, and toxic megacolon may occur in patients with ulcerative colitis [6]. Tolerance, in this situation develops very slowly, as well as other smooth muscle effects. Loperamide is a synthetic agent, does not cross the blood brain barrier, used as an antimotility drug. All opioids are reported to increase bile duct pressure, with a spasmogenic action cause contraction of the sphincter of Oddi with effects on doses dependent activity [6]. Pethidine also, produces smooth muscle contraction via a direct action. Opioids effects on the biliary tract can be reversed by naloxone, nitroglycerine and glucagon.

Other effects on the smooth muscle target the genitourinary system, often leading to urinary retention and urgency. This effect is predominant in elderly and when administered neuraxially. This later feature explains a centrally mediated mechanism of action via receptors located at the sacral spinal cord.

There are some others centrally mediated opioids effects. Some of these are of no clinical benefit and usually unpleasant. Often, opioids may trigger pruritus with various ranges of severity, with mechanism of action not fully discovered. The pruritus predominantly affects nose, face and chest being independent of histamine release. Substituting opioids agents will decrease the incidence. Studies has shown that low dose of naloxone will alleviate this effect. Muscle rigidity is triggered at or just after the loss of consciousness and may manifest from hoarseness in mild cases to impossibility of ventilate in severe situations. It can be minimised by co-administration of induction agents and benzodiazepines. In anaesthetic practice may be prevented by pre-treatment priming with small doses of muscle relaxants. This side effect was reported to be with a higher incidence on concomitant use of nitrous oxide [6]. It is seen more commonly with Fentanyl and its congeners than with morphine and the risk is dose depended. In emergency situation of impossibility of ventilation can be reversed by administration of naloxone.

Opioids agents decrease thermoregulation thresholds, except pethidine, which is a unique in its ability to reduce shivering. Tramadol also has proved to be efficacious in this regard [6].

Histamine release and associated hypotension are variable in incidence and severity, and are with decreased incidence where is a slow IV administration and ameliorated by intravascular fluid loading. This effect is less with fentanyl and its subclass agents, except pethidine. The histamine release may be localised or generalised, often causing facial flushing and variable itch [6].

4.5.1 Opioid-specific effects

Pethidine has been described as a unique agent because of its non-opioid effects. It has a local anaesthetic effect of equivalent potency to cocaine and it has a quinidine-like effect on cardiac muscle to reduce cardiac irritability and arrhythmias [6]. Pethidine overdose produce a complex syndrome characterised by a cardiovascular collapse, seizures, hyperreflexia, mydriasis in addition to a respiratory depression [6].

The use of phenylpiperidines family (except remifentanil) in anaesthesia has been associated with postoperative respiratory depression after high doses, due secondary peaks in plasma levels, possible from the opioids release from the body stores. This action is responsible for the increase in peripheral perfusion and postoperative shivering.

4.6 Pharmacokinetics

4.6.1 Administrations

The choice of route of administration depends on the opioid being utilised, pain severity, the need for agent titration, potential side effects and contraindications to a particular route. The way of administration may activate the onset of peak analgesia and the side effects. For example, respiratory depression may be triggered 7 minutes after an IV dose of morphine, but not until 30 minutes after IM or 6–10 hours after a spinal administration.

There are various degree and length of pain relief effect conferred by certain routes. Spinal administration may produce a greater quality and potentially a longer duration of analgesia, with a lower incident of supraspinal effects. However, an increased incidence of specific side effects (nausea, itching, urinary retention) occurs.

No opioid agonist demonstrates dose-dependent pharmacokinetics. First pass metabolism of orally administrated opioids is made in the liver and the digestive tract wall (up to 50%). Opioids given IM or SC have 100% bioavailability, but peak plasma concentration may be variable up to fivefold influenced by body temperature, site of injection and hemodynamic status. IV administration results in a much restricted rage of plasma concentration [6].

The lung exerts an important first-pass effect on highly lipid-soluble opioids. Prior administration of other lipophilic amines, such propranolol decreases pulmonary uptake, by saturating biding sites [6].

4.6.2 Elimination

Opioids mainly sustain a liver metabolism with a renal excretion of the more hydrophilic metabolites. A few metabolites also take the biliary excretion route. Some amounts of the more hydrophilic agents may be excreted unchanged in the urine. Liver blood flow is the main factor influencing the plasma clearance for most opioids, because of their high hepatic extraction ratio [6].

Morphine. The biotransformation of morphine is unique among opioids agents. Glucuronidation is responsible for 60–80% of its metabolism, and is primarily undergone in the liver with production of high quantity morphine-3-glucoronide (M3G) and only 10% of morphine-6-glucoronide (M6G). The remainder undergoes sulphation (important feature in neonates where glucuronidation metabolism is immature), 5% is demethylated to normorphine, a small amount is converted to codeine, and 10% is excreted in the urine [6, 29]. In healthy subjects up to 10% of glucuronidation occurs in extrahepatic sites, such kidney and intestine. The excretion of the morphine metabolites is directly influenced by the creatinine clearance. 90% of conjugated morphine is excreted in the urine and 10% is excreted in bile, sweat and breast milk. M6G is 2–4 time more potent than morphine and has a longer elimination half-life [29]. Despite being more hydrophilic than morphine, M6G cross the blood-brain barrier, with a longer action due to slower elimination from this site. There is also an entero-hepatic recirculation of morphine and its metabolites, particularly under the chronic oral administration [29].

Diamorphine. Diamorphine is inactive and needs deacetylation in the CSF, liver, and plasma to its final metabolites 6-monoacetylmorphine and morphine. These active metabolites are more hydrophilic, and their ensuing metabolism is as for morphine [6].

Codeine. Codeine is suffering a hepatic metabolization to mainly codeine conjugates and norcodeine, with some urinary excretion of free codeine. Up to 10% of a dose is also metabolised to morphine. This biotransformation is responsible for analgesia produced by codeine. Due to genetic polymorphism, up to 8% of western Europeans are deficient of the enzyme implicated in the liver metabolism. These patients require higher doses, and they may still not experience effective pain relief. Furthermore, the variability may produce dangerous high morphine levels in breast milk [30].

Pethidine. Pethidine metabolism mainly involves hydrolysis to pethidinic acid, with small amount being freely excreted through urine (5%) of the prodrug – although this may be increased up to 25% with urinary acidification (pH < 5) [6]. One third of the metabolism takes the route to N-demethylation to norpethidine, which is finally hydrolysed to norpethidinic acid. Enzyme induction triggered by chronic pethidine use (sometimes also by carbamazepine therapy) induces high levels of transformed norpethidine [6].

Fentanyl and sufentanyl. The high lipid solubility of these agents is responsible for their large volume of distribution, which causes rapid and continued peripheral tissue uptake, limiting initial liver metabolism. This is leading to a greater variability in plasma concentration (13-fold range in fentanyl) during the elimination phase, particularly with fluctuations in muscles blood flow that may be responsible of the secondary peaks in plasma concentration after large doses. Fentanyl, sufentanyl and alfentanyl have a small unchanged renal excretion, being mainly metabolised in the liver. These inactive metabolites are taking the urinary route for excretion.

4.6.3 Patient factors influencing opioid pharmacokinetics and pharmacodynamics

The pharmacokinetics and dynamics of opioids may be altered in a number of physiological states as stated in **Table 8**.

4.7 Opioid drug interaction

This class of pain killers have limited but important interactions with other drugs. Their action is synergistically with other CNS depressant on the level of consciousness. Barbiturates, benzodiazepines and propofol produce effects on the loss of

Physiological states	Effect	Mechanism
Obesity	Overdosage	Central volume of distribution is not reflected by actual body weight Increased volume of distribution prolongs elimination half-life
Infant	Prolonged effect	Decreased conjugation capacity Immature renal function
Elderly	Increased sensitivity to opioid	Decreased neuronal cell mass Decreased central volume of distribution
	Prolonged effect of infusion	Decreased lean body mass with increase adipose tissue is responsible for an increase in total volume of distribution Decreased hepatic blood flow (by 40–50% by age of 75)
Hepatic failure	Increased sensitivity to opioids (in severe liver failure only)	Synergism if encephalopathic Altered integrity of blood-brain barrier Increased elimination half-life for pethidine and tramadol
Renal failure	Morphine toxicity	Accumulation of M6G Possible hydrolysis of glucuronides back to parent compound Uraemia potentiates CNS depression and increases blood-brain barrier permeability

Table 8.
Factors influencing opioid pharmacokinetics and pharmacodynamics.

consciousness with a synergic action from the opioids side and also increase the risk of cardiovascular depression. With anaesthetic use, opioids may decrease the concentration of volatile agents by up to 50% while ensuring amnesia and immobility, with the preservation of hemodynamic stability at low inhaled concentrations (≤1 MAC) [6].

The use of opioids (particularly pethidine and tramadol) with monoamine oxidase inhibitors (MAOI) may lead to serious and potentially fatal consequences as excitatory syndrome (type I) [2, 6]. This is complex syndrome characterised by excitatory phenomena including agitation, fever, rigidity, seizures and coma. This is triggered by the excessive CNS serotonin activity, since both MAOI and pethidine block serotonin reuptake. Rarely also can arise an inhibitory syndrome (type II) characterised by respiratory depression, coma and hypotension, which is the result of MAOI inhibition of hepatic microsomal enzymes leading to a pethidine accumulation.

A similar excitatory syndrome (serotoninergic) is found during the combination of tramadol and serotonin-noradrenaline reuptake inhibitors (SNRIs) [6].

Morphine has been recommended as the opioid of choice for use in these patients.

4.8 Opioid antagonists

The main opioid antagonist currently used in practice is naloxone.

Naloxone is an N-allyl derivate of oxymorphone. It is pure opioid antagonist, without an intrinsic pharmacological activity. It has a high affinity for miu opioid receptors but also blocks other receptors. Naloxone reverses the respiratory depression and analgesia of opioids but also precipitates the withdrawal syndrome in opioids addicts. Naloxone could also block the action of endogenous opioids. IV administration of 200–400 mcg of naloxone will reverse the respiratory depression,

but incremental titration (1.5–3 mcg/kg) is referable in order to minimise the reversal of the analgesic effects of the opioids. Naloxone's action time is roughly 30 minutes, so further doses may be considered to avoid the return of respiratory depression effects of any agonist agent that outlasts the effect of naloxone. Naloxone is also efficient in releasing the pruritus and urinary retention of the intrathecal and epidural opioids. Naloxone has very small oral availability, only 2%, because and major first pass metabolism [6].

4.9 Tramadol

Tramadol is included in the opioids class of drugs, with unique and complex mode of action, only part of which is mediated through opioid receptors. Tramadol is an analogue of codeine and acts as a weak agonist at all types of opioid receptors, with some preference for the miu receptors. It has 10% of the potency of morphine. Tramadol blocks the reuptake of noradrenaline and 5-HT (serotonin) and facilitate the release of the later. By its effects, influences nociceptive transmission activating the descending inhibitory pathways in the CNS. Therefore, Naloxone only partially reverses the analgesic effects of tramadol. Effects on alfa2-adrenergic, NMDA and benzodiazepine receptors may be due to indirect effects secondary noradrenergic system effects [31].

Tramadol is recommended in the treatment of moderate to severe pain. It is well absorbed when given orally, with a bioavailability of 68% and only 20% protein bound. Tramadol is predominantly metabolised in the liver by demethylation and conjugation, with 90% being excreted in the urine. The elimination half-life is 4–6 hours. His metabolites have longer half-life (up to 9 hours) and 2–4 times greater analgesic potency than tramadol and precautions should be taken in hepatic and renal failure.

Tramadol exhibits small risk for respiratory depression when compared with equianalgesic doses of morphine. Also, cardiovascular effects are minimal. There is a low potency for abuse and physical dependence, but still reported. Tramadol's known side effects include: dizziness, nausea, sedation, dry mouth, sweating and skin rashes.

Concomitant use of MAOIs is contraindicated and co-administration with carbamazepine may decrease the concentration and effect of tramadol.

5. General pain management principles

- A - ask about pain regularly
- B - believe the patient's/resident's and family's reports of pain and what relieves it
- C - choose appropriate pain control options
- D - deliver interventions in a timely, logical and coordinated fashion
- E - empower patients

6. Pharmacological intervention

As a result of a nationwide effort to reduce unnecessary opioid use and reduce incidents of patient abuse, clinicians are encouraged to carefully assess their

patient's pain, limit the number of prescribed opioids analgesics and limit further prescribing by evaluating the patient's pain relief and increased functional ability.

The trend to lower usage has had a tremendous impact on opiod use worldwide over the last years. By 2016, paracetamol/hydrocodone, which had been the leading medication prescribed for pain, had dropped from first most prescribed pain medication to the fourth most prescribed drug in the nation, with the volume of prescriptions down to 7.2% in 2015, from 34% in 2012.

In order to facilitate this continuing trend, it is recommended that the following WHO decision ladder and in-depth patient assessment be utilised before requesting or prescribing opioid compounds.

7. Multimodal analgesia

Multimodal analgesia is defined as the use of more than one pharmacological class of analgesic medication targeting different receptors along the pain pathway with the goal of improving analgesia while reducing individual class-related side effects. Evidence today supports the routine use of multimodal analgesia in the perioperative period to eliminate the over-reliance on opioids for pain control and to reduce opioid-related adverse events. A multimodal analgesic protocol should be surgery-specific, functioning more like a checklist than a recipe, with options to tailor to the individual patient.

Elements of this protocol may include opioids, non-opioid systemic analgesics like paracetamol, non-steroidal anti-inflammatory drugs, gabapentins, ketamine, and local anaesthetics administered by infiltration, regional block, or the intravenous route [32–37]. While implementation of multimodal analgesic protocols perioperatively is recommended as an intervention to decrease the prevalence of long-term opioid use following surgery, the concurrent crisis of drug shortages presents an additional challenge. Anaesthesiologists and acute pain medicine specialists will need to advocate locally and nationally to ensure a steady supply of analgesic medications and in-class alternatives for their patients' perioperative pain management.

8. Conclusion

The recommendations are on the basis of the underlying premise that optimal management begins with the patient assessment and development of a plan of care tailored to the individual and the medical status or the surgical procedure involved, with follow-up assessments and adjustments as needed. The evidences support the use of multimodal regimens in many situations, although the exact components of effective multimodal care will vary depending on the patient, setting, and surgical procedure or the medical condition. Therefore, it is important that clinicians consider their patients' pain in the context of: biological, social and psychological factors.

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