13.5 Postoperative pain

Failure to treat postoperative and posttraumatic pain adequately result in increased psychological and physiological stress and contributes to the development of *chronic pain*. Perioperative clinicians are the most experienced in the management of postoperative pain and their experience in this scenario has been extrapolated to guide pain control in most other medical scenarios, including the outpatient department, emergency department, and the ICU.

Day case surgery also warrants specific mention. The incidence of severe pain following these surgeries is approximately 5%. However, inadequate pain control is common because of concerns of administering powerful agents to patients who will be discharged soon, and reluctance on the part of staff to delay the discharge process. Orthopaedic, plastic surgery, laparoscopic procedures and hernia repair are common scenarios in which pain control is often inadequate. Patients with an increased BMI, and procedures that requires longer GA, are risk factors for the development of severe pain.

The use of multimodal analgesia, including local and regional anaesthesia, is strongly advocated in the day case scenario where possible. This means that analgesics of different classes or pharmacodynamics are co-prescribed. These different drugs may have additive or synergistic effects, which allows for lowering the doses of the different analgesics (e.g. opioid-sparing).

These low-dose combinations decrease adverse effects. Whenever possible, multimodal analgesia should be prescribed.

Several strategies are used to pre-empt postoperative analgesia. These include neuraxial block (intrathecal LA and/or epidural opioid), nerve block (nerve plexus, peripheral nerves, infiltration or intra-articular LAs), or NSAIDs before incision, and paracetamol and a longer-acting opioid such as morphine sulphate before the end of surgery. Opioid-free anaesthesia (OFA) has been shown to decrease postoperative analgesic consumption.

Acute pain is usually caused by tissue injury which can be managed by using pre-, intra- and postoperative strategies.

13.5.1 Preoperative strategies

Paracetamol, approximately 15 mg/kg p.o., and an NSAID p.o. are cheap and as effective as intraoperative IV formulations. For surgery lasting more than approximately two hours, intraoperative administration of paracetamol is probably more effective. A long-acting NSAID, such as naproxen/esomeprazole 500/20 mg, is useful. A gapentanoid such as pregabalin 150 mg one hour preoperatively is opioid-sparing, but is associated with postoperative dizziness. If PCA is planned, the use of the device must be explained to the patient.

13.5.2 Intraoperative strategies

Both paracetamol and an NSAID are usually given intravenously intraoperatively. The NSAID is usually administered at induction anaesthesia, while paracetamol is given near the end of surgery, depending on the duration of the surgery. If non-opioid non-NSAID analgesics (e.g. ketamine and dexmedetomidine), form part of postoperative analgesia, these are usually administered at low doses during surgery and continued during the postoperative period. An opioid-free anaesthetic technique decreases postoperative opioid requirements. If IV or epidural PCA is planned, these can be activated before the end of the surgery. An opioid can be started at the end of surgery (e.g. if buprenorphine is prescribed as the postoperative opioid, buprenorphine can be administered IV about 30 minutes before the end of surgery).

13.5.3 The postoperative care unit

If the patient is not transferred to a high care unit (HCU) or the ICU directly from the operating room, immediate postoperative pain control in the postanaesthetic care unit (PACU) in the operating theatre complex is usually accomplished by titrating an IV opioid to an adequate effect. *Morphine sulphate* is usually used at a dose of approximately 50 µg/kg every 5 minutes until VAS has decreased to < 3/10. Other IV opioids can also be used, including oxycodone, tramadol and buprenorphine.

If the patient has not received paracetamol intraoperatively, a dose of 15 mg/kg is immediately given intravenously. This dose of intravenous paracetamol has a morphine-sparing effect of up to 60%; the analgesic efficacy of IV paracetamol 1 g (approximately 15 mg/kg) is similar to 10 mg of IV morphine sulphate over 15 minutes.

Ideally, the first dose of analgesics prescribed on the postoperative prescription should be offered as soon as the patient arrives in the PACU (hopefully, the patient is awake and with no airway in situ). This practice will ensure a smoother transition of analgesia from theatre to ward, since it often occurs that the postoperative analgesics are not fetched from the pharmacy for several hours after the patient has arrived back in the ward. Any analgesic for postoperative pain administered intraoperatively and in the PACU must be documented on the postoperative prescription to prevent overdosage when the patient is transferred to the ward.

13.5.4 The postoperative prescription

The postoperative prescription should follow the same principles given in the analgesic ladder earlier. For moderate to severe pain, the prescription should include paracetamol, an NSAID, as well as an opioid.

Paracetamol

Paracetamol is safe in almost every clinical scenario. On its own, it is effective for mild to moderate postoperative pain at the most. Paracetamol improves analgesia when prescribed with other analgesics. However, evidence is conflicting and the efficacy of combinations seems to depend on the type of surgery and the doses of analgesics used in combination with paracetamol. For example, in surgery complicated by severe pain (e.g. spinal surgery), the role of paracetamol is less clear. Paracetamol and NSAIDs have at least additive analgesic effects. Therefore, this combination is more effective than the individual drugs. Combinations preparations containing paracetamol, an NSAID (usually ibuprofen) with or without codeine, is useful for mild to moderate pain. It should be noted that the contribution of paracetamol to the analgesia offered by a high dose of NSAIDs may be negligible. The lower-dose combination of paracetamol and tramadol is as effective as higher doses of either drug.

The dose of the oral and IV formulations is 15 mg/kg 6-hourly, but 8-hourly in patients with kidney or liver impairment. Care must be taken not to exceed the maximal IV dose of approximately 15 mg/kg 6-hourly or 60 mg/kg/day, especially in elderly patients and patients with decreased liver function. The analgesic efficacy of IV paracetamol 1 g (approximately 15 mg/kg) is similar to 10 mg (0.15 mg/kg) of IV morphine sulphate over 15 minutes. Although usually not adequate for severe pain, the opioid-sparing effect of IV paracetamol is useful in patients who can be discharged. The lack of adverse effects or sedation is of benefit to patients

who remain in hospital. If paracetamol was administered pre- or intraoperatively, it must be recorded on the prescription chart to prevent an overdose postoperatively.

Although IV paracetamol has been shown to be opioid-sparing, oral paracetamol strictly scheduled (6-hourly) is not necessarily inferior to IV paracetamol. When paracetamol forms part of multimodal analgesia, the IV route does not produce better analgesia than the oral preparation. Although *IV* propacetamol achieves therapeutic levels quicker than tablets, analgesia was not better at 30 minutes; however, it was better two hours after oral paracetamol. Effervescent tablets halve the time to peak blood levels as compared to conventional tablets. Therefore, paracetamol should form part of multimodal analgesia, but IV paracetamol should be reserved for patients in whom the enteral route (including the oral, nasogastric or gastrostomy) is not accessible. Oral formulations (including effervescent tablets) are far cheaper than the IV formulations.

NSAIDs

NSAIDs should, if not contraindicated (see below), form part of multimodal analgesia. Although these drugs form a definite and very useful part in the treatment of pain, notice must be taken of important adverse effects. The discussion that follows is to emphasise the group adverse effects of NSAIDs. These belong to a diverse group of drugs that are analgesic, antipyretic and anti-inflammatory. To appreciate its adverse effect profile (and one side effect used therapeutically as antiplatelet agents), its group pharmacodynamics (its effect on body systems) must be appreciated. NSAIDs affect prostanoid production throughout the body.

Cyclooxygenase

Phospholipase A2 (PLA2) enzymes are a group of enzymes that occur in all tissues. These occur intra- and extracellularly and are activated by diverse stimuli, such as cell membrane injury. PLA2 cleave fatty acid from phospholipid to form arachidonic acid (AA). The cyclooxygenase (COX) and peroxidase activities of the COX isoforms COX-1 and COX-*2* change AA to PGG2 and PGG2 to PGH2. Tissue-specific isomerases and synthases transform PGH2 to the three groups of prostanoids: *prostaglandins* (PGE2, PGF2α and PGD2), *PGI2* (prostacyclin), and *thromboxane A2* (TXA2).

The production (stimulus, type and output) of a particular PG by particular cells depends on the expression of the particular COX enzyme (COX-1 and COX-2) and of the particular enzymes distal to PGH2 to render the different cell-specific prostanoids.

The different prostanoids interact with its respective cell-membrane receptors occurring in different tissues where these play important tissue-specific physiological functions and pathophysiological responses. These include:

- Fever (PGE2), modulation of fever and inflammation (PGE2) and its resolution (including erosion of cartilage and juxta-articular bone)
- Haemodynamics (including coronary artery blood flow and ischaemia and renal hemodynamics (PGI2) and progression of kidney disease)
- Renal water and electrolyte homeostasis (PGE2) and oedema formation
- Gastric and intestinal (GI) cytoprotection (PGE2 and PGI2) and ulceration
- Haemostasis (TXA2 and PI2) and thrombosis
- Embryo implantation, uterine function and labour (PGF2α)
- The sleep cycle (PGD2)
- Anti-atheroma effect and progression of atherosclerosis
- Angiogenesis and cancer

COX-1 *is expressed constitutively* (it is active all the time) in most cells. It has a housekeeping function in homeostasis and is not normally inducible. From a therapeutic viewpoint, COX-1 has important functions regarding GI cytoprotection and platelet activation.

Platelet COX-1

COX-1 is the only COX present in mature platelets. AA is released when thrombin and adenosine diphosphate (ADP) interact with their specific platelet receptors. COX-1 transforms AA to PGH2, which isomerises to TXA2. TXA2 causes platelet aggregation, is a potent vasoconstrictor, and promotes vascular smooth muscle proliferation.

Low-dose aspirin irreversibly and almost completely (> 95%) inactivate COX-1 activity resulting in decreased platelet function for the duration of the life of the platelet (i.e. approximately ten days). Since even a very low concentration of TXA2 activates platelets, complete (> 95%) and continuous suppression of platelet COX-1 is essential for cardio-protection. Therefore, the traditional non-selective COX blockers (tNSAIDs), which reversibly, incompletely and intermittently inhibit platelet COX-1, are not cardio-protective. The exception is naproxen. At a high dose of 500 mg bd (which is the therapeutic dose), it inhibits platelet COX-1 > 95%, even at the end of the 12-hour dosing interval.

The use of NSAIDs does not significantly increase postoperative bleeding or the need for blood transfusion. Regarding aspirin withdrawal, the risk and benefit of stopping the drug should be assessed. If low-dose aspirin is used for the secondary prevention of CV events, patients should continue taking aspirin perioperatively. Withdrawing aspirin may increase the risk of serious thromboembolic complications. Usually, continuing with aspirin carries a minimal risk of perioperative bleeding, as compared to the risk of developing thromboembolic complications when aspirin is withdrawn. Procedures where the risk of withdrawal of aspirin is

justified include intracranial, middle ear, posterior segment of the eye, intramedullary spinal, and perhaps transurethral prostatectomy surgery.

Gastric COX-1

The protection of gastric mucosa by PGs is mediated by inhibition of acid secretion and increased production and secretion of mucus, bicarbonate and surfactant-like phospholipid. PGs also promote healing of gastric lesions. This function is mediated by hepatocyte growth factor (HGF) expressed in gastric mucosal cells. HGF stimulates gastric epithelial growth as well as the maintenance of gastric mucosa.

COX-1 is expressed constitutively in gastric mucosa. It is responsible for the production of the cytoprotective prostanoids PGE2 and PGI2. Gastro-duodenal ulceration in many patients taking tNSAIDs is ascribed to suppression of COX-1 activity. Although the inhibition of mucosal COX-1 is responsible for ulceration, the high grade inhibition of platelet COX-1 by tNSAIDs in some patients is responsible for serious haemorrhage, which may be fatal. Selective COX-2 inhibitors have a better safety profile since these spare both mucosal and platelet COX-1 activity. Therefore, the GI advantage of COX-2 selective inhibitors (coxibs) is lost when patients receive low-dose aspirin.

Regarding gastric cytoprotection, both COX-1 and COX-2 are essential in mucosal defence, where each has specific functions under various physiological and pathophysiological conditions. In normal gastric mucosa, inhibition of neither COX-1 nor COX-2 induces gastric lesions, but during pending injury (e.g. when the mucosa is exposed to acid), inhibition of COX-1 but not of COX-2 leads to mucosal lesions.

COX-2 *occurs both constitutive and inducible* (mostly). Expression of COX-2 is low under basal physiological conditions. It is *constitutively* expressed in several tissues, notably the kidney and brain. Therefore, COX-2 has regulatory functions under basal physiological conditions and does not only catalyse the production of mediators under nonbasal pathophysiological conditions (inducible).

COX-2 is induced in various cells, including monocytes, macrophages and endothelium. COX-2 is induced at sites of inflammation, infection and cancer. Induction occurs in response to inflammatory cytokines, endotoxin, vascular laminar shear stress and growth factors. The products of COX-2 activity include PGE2 and prostacyclin. In both physiologic and pathologic conditions, COX-2 is the rate-limiting enzyme in PGI2 biosynthesis. PGE2 and prostacyclin (PGI2) are involved in a variety of physiological and pathophysiological processes, such as renal haemodynamics, blood pressure control, resistance of the endothelium to thrombosis, pain, and triggers of inflammation, such as endotoxin.

COX-2 is involved in GI mucosal protection in concert with other factors, such as NO and afferent nerve function. Severe mucosal lesions develop when COX-2 is inhibited when the function of any one of these defence mechanisms is compromised. **Moreover, isolated COX-2 inhibition harms gastric mucosa during ischaemia-reperfusion** (an ubiquitous phenomenon during haemodynamic instability, when periods of hypoperfusion alternates with periods of reperfusion). This suggests that COX-2 is upregulated to attenuate ischaemia-reperfusion-induced injury. This effect is ascribed to the effect of the products of COX-2 on the regulation of cytokine release by inflammatory cells.

The interaction between the effect of Helicobacter pylori and COX-2 should be remembered. The gastric mucosal toxicity of *H. pylori* infection involves release of inflammatory cytokines including IL-1, IL-6, IL-8 and TNFα. These cytokines increase vascular permeability, and leukocyte infiltration. *H. pylori* also stimulates gastric mucosa fibroblasts to produce COX-2 and PGE2. The latter probably stimulates production of HGF by gastric fibroblasts. Therefore, the bacterium induces the production of PGE2 and HGF, which decreases its mucosal toxicity. This counterbalance balance is called chronic gastritis and may be present without destruction of the mucosa. However, this counterbalance is easily disturbed by the inhibition of PGE2 and HGF production resulting in ulceration. This is probably the pathophysiology of NSAID-induced GI ulceration.

COX-2 selective inhibitors suppress PG and HGF released by gastric fibroblasts to the same degree as the non-selective COX inhibitors (tNSAIDs) and since COX-2 is important in the healing of gastric ulcers, these delay ulcer healing to the same degree as the non-selective inhibitors (tNSAIDs) do. The ulcer-preventing balance between the noxious effect of *H. pylori* toxicity (ulceration) and the protecting effect of PGE2 and HGF from gastric fibroblasts (cytoprotection and healing) is disturbed. Therefore, both tNSAIDs and selective COX-2 inhibitors swing the scale in favour of ulceration and delayed ulcer healing.

Endothelial cells form a dynamic barrier which reacts to local and systemic stimuli, such as platelets and inflammation as well as shear stress, generated by pulsatile blood flow along the arterial network. COX-2 is up-regulated by physiological laminar shear stress stimulation.

Endothelial COX-2 controls the production prostacyclin, PGD2 and PGE2 of which *PGI2* is the most important prostanoid in the macrocirculation. Prostacyclin regulates the activation of circulating blood cells and underlying smooth muscle cells. It is a potent inhibitor of platelet aggregation, platelet TXA2 production, leukocyte-endothelium interactions, and vascular smooth muscle proliferation. It is a potent vasodilator that antagonises the vasoconstriction caused by TXA2.

Selective COX-2 inhibition is associated with an increased risk of MI, especially in patients (phenotype) who are dependent on the availability of PGI2 (vasodilatation and decreased

platelet function). If these patients receive coxibs over a long time, an initial low risk for or stable ischaemic heart disease and peripheral vascular disease may lead to accelerated development of CV disease. Therefore, selective inhibition of COX-2-dependent endothelial PGI2 without inhibition of platelet COX-1 (production of TXA2) results in an increased CV risk. Dose reduction of these agents decreases their anti-inflammatory and analgesic efficacy. This is particularly important in vasculopaths, especially when presenting for surgery, including vascular surgery.

In the kidney, constitutive COX-2 is involved in renal perfusion and glomerular blood flow. In the medulla, it plays a crucial role in the regulation of a cardioprotective gene networks, which fulfils an important role in the CV adverse effects of NSAID (cardiorenal adverse effects). COX-2 inhibitors increase blood levels of asymmetrical dimethylarginine (ADMA), a naturally occurring endothelial nitric oxide synthase (eNOS) inhibitor, which contributes to the CV adverse effects of NSAIDs. These include the development of new hypertension and deterioration of renal function, especially in patients with underlying renal failure, hypertension, concomitant treatment with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonists (ARA), and elderly patients.

Pharmacodynamic classification of COX inhibitors

The COX-1 and COX-2 selectivity of NSAIDs are determined by measuring its IC50s. The IC50 is the concentration of the drug to decrease the activity COX-1 and COX-2 by 50%. The lower the IC50, the more selective (a low concentration can inhibit the particular COX); the higher the IC50, the less selective (a higher concentration is needed to inhibit the particular COX). From these findings COX-1/COX-2 IC50 ratios were calculated. Therefore, the lower the COX-2s IC50, the higher the COX-1/COX-2 IC50 ratio and the higher COX-2 selectivity.

These ratios demonstrate that selectivity is a continuum; from pure COX-1 to pure COX-2 selectivity. In between selectivity varies between balanced (non-selective) blockers, such as the tNSAIDs ibuprofen, ketoprofen, flurbiprofen and naproxen towards COX-1 and COX-2 activities. However, the group of COX-2 selective (COX-2 CI50 < COX-1 CI50) also includes the tNSAIDs meloxicam and diclofenac. In vitro, the IC50s of *diclofenac* indicates that it is approximately 29 times more COX-2 than COX-1 selective. Regarding the selective COX-2 inhibitors (coxibs) the ratios vary: celecoxib 30, valdecoxib (the active metabolite of parecoxib) 61, rofecoxib 272, and etoricoxib 344. However, plasma concentrations necessary for therapeutic effect may be much higher than their in vitro IC50s (e.g. daily doses of ibuprofen and naproxen inhibit both COX-1 and COX-2 by 80% [not 50%]). Similar observations have been made regarding COX-2 selective inhibitors.

Note that *diclofenac* has a ratio of 29 and *celecoxib* of 30. These also demonstrate similar pharmacodynamics; namely, these do not affect the antiplatelet effect of low-dose aspirin, and display similar long-term GI and CV adverse effects.

All the NSAIDs increase the alternative pathway from AA to leukotrienes. Leukotrienes, also involved in inflammation, are powerful bronchoconstrictors and increase vascular permeability causing tissue oedema. Leukotrienes are involved in allergic reactions, rhinitis and asthma.

Cross-hypersensitivity to NSAIDs (including aspirin) may exist. Patients at risk to develop allergic reactions include asthmatics and patients suffering from rhinitis, as well as patients with nasal polyps. Allergic reactions are more common in NSAIDs with sulphonamide in its molecule, including all the oxicams and coxibs.

From the above discussion, it should be clear that NSAIDs, from tNSAIDs (balanced COX-1/COX-2 inhibitors) to selective COX-2 inhibitors, should be prescribed taking into account (patho) physiological and pharmacological factors in the particular patient.

The patients who are at risk are the following:

- Those with any cardiac disease (elderly, ischaemic, failure).
- Those with any vascular disease or haemodynamic disorders (elderly, hypovolaemia, dehydration, hypertension, atherosclerosis, peripheral arterial disease, cerebrovascular disease, renovascular disease, diabetes mellitus). NSAIDs should not be administered pre- or intraoperatively if conditions are foreseen that will cause intraoperative haemodynamic instability (especially hypotension), particularly in patients with preexisting vital organ disfunction. These conditions include use of antihypertensive agents (ACEIs, ARAs and diuretics), and hypovolaemia. Intraoperative conditions include large fluid shifts, the type of surgical intervention (e.g. aortic cross-clamping), deliberate hypotension, and administration of IV radiocontrast. All these conditions may compromise vital organ function in patients with premorbidity – in particular myocardial ischaemia, kidney failure and liver failure. NSAIDs should not be administered intra- or postoperatively in patients undergoing free flap surgery since they have been implicated in flap failure (thrombosis of the vascular pedicle).
- Those with any renal disease, including elderly patients, hypertension, diabetes, hypovolaemia or dehydration (physical exertion, such as running). Remember the dangerous triad NSAID + diuretic + ACEI/ARA.
- Those with a history of gastritis or GI ulceration (consider coprescribing a PG [misoprostol], a proton pump inhibitor [PPI] [esomeprazole], or an H2-blocker [ranitidine]).
- Those with a history of rhinitis or asthma.
- Those with bleeding disorders (concomitant use of antithrombotic agents and anti-platelet agents). These drugs are not contraindicated in patients taking low-dose aspirin or on thromboprophylactic low-molecular-weight heparins (LMWHs). In fact, low-dose aspirin protects against the CV side effects of the coxibs – but eliminates its (alleged) GI advantage. Since all the NSAIDs are highly plasma protein bound, it can displace warfarin from albumin, which increases the free fraction of warfarin resulting in an increased INR. Moreover, a low plasma protein level increases their free fractions, which increase their toxicity. This should

be taken into account in patients that undergo haemodilution (resuscitation fluids, fluid retention).

- NSAIDs should be avoided in pregnancy, especially during the first and third trimester.

Pharmacokinetics of NSAIDs

The pharmacokinetics of NSAIDs vary between and within chemical groups. In general, the following principles should be remembered:

- These are acids.
- These are absorbed from the stomach where it can cause local irritation. Therefore, these should be taken with food, although food may dilute the drug, which may delay absorption. **However, its effect on cytoprotection is a systemic effect and is not prevented by IV or rectal administration.**
- These are highly plasma protein-bound (mainly albumin). Therefore, these drugs have a low volume of distribution (Vd). Therefore, doses should be calculated according to ideal or lean body mass. Moreover, these can displace other highly protein-bound drugs, notably warfarin and oral hypoglycaemic agents (the sulphonylureas).
- These are metabolised in the liver to inactive metabolites and excreted by the kidneys. Therefore, if used at all, patients with significant liver and kidney impairment should not receive these drugs.
- Elderly patients have a lower lean body mass, decreased clearance of drugs and should therefore receive lower doses.

Analgesic equivalence of NSAIDs and routes of administration

NSAIDs have similar analgesic effects at equivalent doses and are useful for the treatment of acute moderate to severe pain, and provide better analgesia during mobilisation than opioids. Regarding bone fractures and orthopaedic procedures, little evidence supports a detrimental effect of NSAIDs on bone healing, but these should be limited to a few days.

NSAIDs are all opioid-sparing and lack the adverse effects of opioids, namely sedation, nausea, vomiting, dizziness and confusion – the latter two especially in elderly patients.

Not all the analgesic effects of NSAIDs are explained by its effect on peripheral nerve endings, that is at the site of injury. These also affect COX activity in dorsal root neurons (afferent neurons) outside the blood–brain barrier (BBB), as well as in the CNS (spinal cord and brain) inside the BBB. Since most of these agents are highly hydrophilic, the latter mechanism has been questioned. However, diclofenac affects dorsal root neurons and parecoxib crosses the BBB and may contribute to analgesia – similar to that of paracetamol.

An NSAID may be administered preoperatively (p.o. or IV; in the ward or during induction of anaesthesia) or intraoperatively. Preoperative administration attenuates the inflammatory response before tissue injury starts and may contribute to better postoperative analgesia and mobilisation. Etoricoxib 1.5 mg/kg (90–120 mg) p.o. preoperatively is an effective analgesic for more than 20 hours.

Postoperatively, it is unnecessary and expensive to continue with IV NSAIDs. If a patient is NPO and receives IV fluids only, the safety of any NSAIDs is questionable. Several NSAIDs can be given p.o., IV, IM, as well as rectally, topically, as surgical site infiltration and intra-articularly. The route of administration does not affect its efficacy and adverse effect profile. However, the latter three applications provide better analgesia with lower drug blood levels.

The following NSAIDs can be administered IVI:

- *Ketorolac* is a balanced (COX-1:COX-2) inhibitor. It is available in both IV and oral formulations. The dose is 0.5 mg/kg (one 30 mg injection) followed by about 0.15 mg/kg (one 10 mg injection) 6-hourly, with a maximum of about 1 mg/kg/day (0.8 mg/kg/day in the elderly).
- *Lornoxicam* is a balanced (COX-1:COX-2) inhibitor. It is available in both IV and oral formulations. The IV dose is 0.1 mg/kg bd.
- *Parecoxib* is a COX-2 selective inhibitor available as injection only. The dose is 0.5 mg/kg followed by 0.5 mg/kg 12-hourly.
- *Diclofenac* can be given IV as a **buffered solution** over 15–60 minutes – **no bolus IV injection**. The LD is 0.5–1.0 mg/kg in 200 ml of a **buffered solution**, followed by an infusion of 70 μg/kg/h not exceeding a dose of 2 mg/kg/hour. The buffered solution is prepared as follows: add 0.5 ml of an 8.4% sodium bicarbonate injection (or 1 ml of 4.2%) to 200 ml of sodium chloride 0.9% solution or glucose 5% solution. Discard the solution if crystals or precipitates are observed after the addition of diclofenac.

The following oral (or rectal) NSAIDs are useful postoperatively:

- *Diclofenac:* 0.7 mg/kg 8-hourly with a maximum of 2 mg/kg/day. In patients with a history of peptic ulceration, the diclofenac/misoprostol combination is safer.
- *Lornoxicam:* 0.1 mg/kg 12-hourly; a fast-acting tablet is available.
- *Ibuprofen:* 4–5 mg/kg 6-hourly to a maximum of 20 mg/kg/day. Several combinations with paracetamol and paracetamol as well as codeine are available.
- *Naproxen* is a balanced COX-1/COX-2 inhibitor. Different from other tNSAIDs, it blocks platelet COX-1 activity > 95%, which decreases CV risk. This anti-cytoprotective gastric effect is prevented by the co-formulation with esomeprazole. *Naproxen/esomeprazole 500/20 mg* is taken 12-hourly and it can be given preoperatively.
- *Etoricoxib:* 1–2 mg every 24 hours and it can be given preoperatively.

Dexamethasone

Glucocorticoids are anti-inflammatory by blocking PLA2, which prevents the formation of AA, and therefore of PGs. This glucocorticoid is a potent, long-acting steroid that is also used as part of multimodal antiemetic treatment postoperatively. A single antiemetic dose of approximately 0.15 mg/kg at induction, is opioid-sparing for at least 24 hours. It has not been associated with glucocorticoid adverse effects.

Opioids

Opioids are used to treat moderate to severe pain. Opioids are often prescribed 'when necessary' for fear of accumulation and respiratory suppression. On the other hand, prescribing an opioid at fixed intervals may result in opioid plasma levels that vary between excessive (overdose) and insufficient (pain). This problem may be overcome by PCA, constant drug infusion and sustained-released drug formulations. The former two methods should preferably be offered in HCUs where patient surveillance is more reliable.

All the opioid agonists (morphine, codeine, dihydrocodeine, oxycodone), buprenorphine, a dualist (tilidine), and atypical opioids (tramadol and tapentadol) are widely used in a wide variety of pain scenarios. Buprenorphine at lower doses (such as used for postoperative analgesia) is a potent agonist (about 30 times more potent than morphine), but it is a dualist/antagonist at high doses. However, **all of these share the same dose-dependent dangers (respiratory depression, sedation, hypotension) and troublesome adverse effects (nausea and vomiting, constipation). All opioids are addictive** *(except dualist buprenorphine that is used in opioid addicts).* The sedative effects of this group of analgesics should be taken into account in patients with a history of OSA. All opioids suppress respiration and should be prescribed cautiously in a patient who is dependent on the central drive of respiration by CO_2 (lung disease) or with increased intracranial pressure. Morphine releases histamine, causing a maculopapular rash along the vein if given IVI, or at the site of injection if given subcutaneously. The histamine may provoke bronchospasm in sensitive patients.

What dose of opioid is prescribed?

Doses should be individualised to provide adequate analgesia at the smallest dose to minimise adverse effects. This strategy decreases the adverse effects and misuse. Respiration and blood pressure should be closely monitored for the first 24–72 hours and following dose increases.

Co-prescribing different opioids may theoretically be justified (e.g. a μ agonist such as morphine plus a μ and κ agonist such as oxycodone). However, this combination has not proven useful. Combining different opioids should be avoided. On the one hand, its intrinsic activity (full agonist or dualist) at, and affinity for, opioid receptors may differ. Therefore, the effect of two agonists may be increased (more adverse effects), or the effect of a dualist with a high

affinity may decrease the effect of the full agonist. However, opioids which act on more than one opioid receptor may have favourable effects. Oxycodone (μ + κ agonist + serotonin agonist) may be a better analgesic for visceral pain. The combination of buprenorphine and tramadol have an additive analgesic effect and improved analgesia in a patient with an opioid abuse disorder stabilised on buprenorphine (usually transdermal patch).

Tramadol deserves some comment. Tramadol is a serotonin and noradrenaline reuptake inhibitor and releaser. It is a weak opioid and often regarded as a safe opioid with fewer adverse effects and addiction potential. However, the active metabolite of tramadol is a potent opioid responsible for the risk of abuse, where short-term use becomes prolonged abuse, similar to other opioids.

The parent drug tramadol is a weak opioid, while the analgesic effect is related to the inhibition of norepinephrine and serotonin reuptake. However, in the liver, it is metabolised to desmetramadol (O-desmethyltramadol) by the CYP2D6 enzyme. The affinity of desmetramadol for μ-receptors is 700 times greater than that of tramadol, and is similar to that of morphine, and is responsible for its abuse potential.

Polymorphisms of CYP2D6 influence the metabolism of tramadol to desmetramadol and varies from 3% in poor metabolisers to 86% in extensive metabolisers. Therefore, the extensive metabolisers may be more prone to addiction to tramadol. Although tramadol is a Schedule 5 drug, demetramadol is an opioid similar to morphine and oxycodone, which are Schedule 6 opioids. Therefore, the number of tramadol capsules and tablets on discharged prescriptions should be limited to not more than 10 units.

- *Codeine* on its own is a poor analgesic. Approximately 10% is metabolised to its active metabolite morphine. This metabolic path is under genetic control and much larger fractions may be metabolised to morphine. Therefore, the analgesic activity is unpredictable. It is usually included in analgesic combinations with paracetamol and an NSAID, such as ibuprofen.
- *Morphine chloride* oral solution (1, 2 and 5 mg/1 ml). *The oral dose* is approximately 25 μg/kg 4-hourly.
- *Morphine sulphate* injection (10 and 15 mg/ml). The IV dose is 50 μg/kg every 5 minutes until the VAS is < 30/100 mm. This is followed by an infusion of approximately 50–100% of the titrated dose/hour and titrate down or up by approximately 15%. The dose varies between 50 and 300 μg/kg/h.
- *Tramadol* (50 and 100 mg capsules and injection). IV loading (if necessary) with up to 1.5 mg/kg followed by 0.7 mg/kg every 30 minutes up to a maximum of 3 mg/kg. This is followed by 0.7–1.5 mg/kg 4–6-hourly p.o. (or intravenously) to a maximum of 8 mg/kg/day.
- *Tapentadol* (50 and 100 mg tablets). 0.7–1.5 mg/kg 4–6-hourly.

- *Buprenorphine* (0.2 mg [200 µg] and 0.4 mg [400 µg] SL tablets and 0.3 mg [300 µg] injection). The dose is 3–5 µg/kg sublingually or intravenously 6–8-hourly.
- *Tilidine* (50 mg capsules and drops with 2.5 mg/drop). The dose is 0.8 mg/kg 6-hourly.
- *Oxycodone hydrochloride*. Oxycodone base and morphine base are approximately equipotent. Oxycodone HCl 10 mg Oxycodone base 9 mg.
- Immediate-release tablets (5, 10 and 20 mg): 0.07–0.15 mg/kg 4–6-hourly.
- Prolonged-release tablets (5, 10, 20, 40 and 80 mg). This preparation is not indicated for acute postoperative pain, but for palliative care. The dose (according to the level of tolerance) is one tablet 12-hourly.
- SR tablets with oxycodone/naloxone 5/2.5 mg, 10/5 mg and 20/10 mg. Naloxone has an oral bioavailability of less than 2% and blocks opioid receptors in the GIT. It is included to counteract constipation (opioid tolerance does not develop to constipation) and to prevent IV abuse. The tablet releases oxycodone in two peaks; one at approximately 40 minutes and at 7 hours. The dose is approximately 0.3–0.6 mg/kg around the clock 12-hourly.
- For breakthrough pain, the 0.7 mg/kg 4-hourly of the short-acting oxycodone can be given in between, keeping in mind the peak delivered by the SR tablet is at about 7 hours. The maximum dose is approximately 1.0 mg/kg 12-hourly.
- *Oxycodone injection*. 10 mg oxycodone chloride is titrated postoperatively and maintained in an HCU or the ICU. The titration dose is 50–100 µ/kg over 2 minutes. This dose can be given 4-hourly or followed by an infusion of approximately 2 mg/hour (approximately 25 µg/kg/h.

Please note: sedatives are not analgesic and should not be co-prescribed with opioids.

The following drugs and drug combinations should be avoided:

Pethidine is a dirty drug renowned for nausea and vomiting as well as increase in heart rate and increased peripheral resistance. Moreover, its active metabolite accumulates in patients with renal failure.

Sedation, delirium, *hypotension and dizziness* may be troublesome and dangerous in *elderly patients*. Falls in these patients give rise to head injury and fractures. There is a significant association between hip fractures and elderly patients receiving *tramadol or meprobamate*.

Sedatives such as the benzodiazepines suppress the *peripheral drive of respiration* in the carotid body and aortic arch by a low arterial PO_2 and acidosis. Therefore, co-prescribing opioids and benzodiazepines can cause *severe respiratory suppression*.

Sedatives in analgesic combinations are unnecessary and dangerous. These include the sedative antihistamines such as hydroxyzine, doxylamine, and phenothiazines such as promethazine, and the anxiolytic meprobamate. These sedatives cause sedation and delirium, especially in

elderly patients, which contribute to falls. ***Meprobamate is addictive and has been withdrawn from the market in Canada and Europe***.

Sedatives increase the risk of respiratory complications, especially in elderly patients, obese patients, and patients with OSA (enquire about snoring).

Tramadol should not be prescribed for patients receiving an SSRI, serotonin and noradrenalin reuptake inhibitor antidepressants (SNRIs), or monoamine oxidase inhibitor (MAOI). Tramadol in combination with an SSRIs can give rise to hyperserotoninergic syndrome (HS) that can be fatal. Tapentadol has also been implicated. Although sertraline inhibits the transformation of tramadol to its active metabolite, which is responsible for its effect on μ-receptors, the serotoninergic and noradrenergic mechanisms of analgesia is not affected. Other analgesics with serotoninergic effects and which have also been implicated are fentanyl, oxycodone, pethidine, codeine, buprenorphine and ketamine. Although HS is not often diagnosed, it should be considered in patients receiving analgesics and presenting with a change in mental status, increased muscle tone or autonomic instability.

The diagnosis of HS is made in a patient who has received serotonergic agents and may vary from subtle psychiatric signs to the complete life-threatening syndrome.

HS is a triad of clinical signs consisting of the following:

- *Mental status and neurological signs:* restlessness, confusion, anxiety, agitation, hypomania, hallucinations, convulsions and coma.
- *Neuromuscular:* muscle rigidity, trismus, tremors, hyperreflexia, myoclonus, ocular clonus, nystagmus and ataxia.
- *Autonomic instability:* tachycardia, hyper- or hypotension, tachypnoea, diarrhoea, mydriasis, sweating and hyperthermia.

Management of HS consists of discontinuation of the suspected agents, administration of antiserotoninergic agents (oral cyproheptadine or IV chlorpromazine), sedative-anticonvulsants such as a benzodiazepine, neuromuscular blockade, and intubation and ventilation.

Being a serotonin agonist, tramadol causes severe nausea in some patients. The analgesic effect of tramadol is antagonised by the 5-HT3 receptor antagonist antiemetics, such as ondansetron.

The sedative effect of other opioids is increased by MAOIs and patients may fall into a deep coma.