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Nonsteroidal anti-inflammatory drugs (NSAIDs)

By the perioperativeCPD team

Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications that relieve or reduce pain. Their actions are analgesic, anti-inflammatory and antipyretic. The most popular examples of drugs in this group are aspirin, ibuprofen and naproxen. Estimates suggest that about 30 million people around the world use NSAIDs every day.

Perioperatively, using NSAIDs avoids many of the adverse effect of opioids such as respiratory depression, sedation, nausea and vomiting and gastrointestinal stasis. Although an effective analgesic they have significant adverse effects and contraindications which the perioperative practitioner must be aware of.

A very brief history

The first NSAIDs were called salicylates and were derived from the bark of the willow tree. Aspririn or more correctly Acetylsalicylic acid was first produced in 1853. Paracetamol which is not a NSAID but closely related was first used in 1893. Ibuprofen, an analogue of aspirin, was discovered in 1961 by Stewart Adams and John Nicholson while working at Boots UK Limited and initially marketed as Brufen.

What are the different NSAIDs?

Some NSAIDs are available 'over the counter' from pharmacies and other retail outlets and, as a result, they tend to be thought of as 'mild' or 'weak' analgesic agents. Other NSAIDs are available only on prescription (Table 1).

	Prescription	Available from pharmacy
Aspirin	✓	✓
Celecoxib	✓	
Diclofenac	✓	✓ but only in low doses
Ibuprofen	✓	✓
Indomethacin	✓	
Mefanamic acid	✓	
Meloxicam	✓	
Naproxen	✓	✓ but only in low doses

Table 1: **Some commonly used NSAIDs**

Although widely used, studies have revealed that the side-effect profile of NSAIDs is significant, particularly within the gastrointestinal and cardiovascular systems. Therefore, to use these drugs safely, healthcare professionals must be aware of the clinical status of the patient when prescribing or administering these drugs.

It is also important that you understand how NSAIDs work and how the side-effects occur, so you can anticipate and maybe prevent potential side-effects.

Warning: There is a possible link between aspirin and Reye's syndrome in children. Reye's syndrome is a very rare condition that can cause serious liver and brain damage. Never give aspirin to children under 16, unless their doctor prescribes it.

What Is Pain?

First, it helps to understand what pain is. On a basic level, pain is the result of an electrical signal being sent from your nerves to your brain. But the process is not only electrical. When you get injured, say with a cut, the damaged tissue releases numerous chemical mediators including prostaglandin. These prostaglandins cause the tissue to swell. They also amplify the electrical signal coming from the nerves. Basically, they increase the pain you feel.

If you are not familiar with pain pathways we suggest you start with our module 'An introduction to pain pathways'.

What exactly are prostaglandins?

Prostaglandins are a group of lipids with hormone-like actions that the body makes primarily at sites of tissue damage or infection. There are several different types of prostaglandins and prostaglandin receptors that affect almost every part of your body. The effect of prostaglandins depends on multiple factors, including:

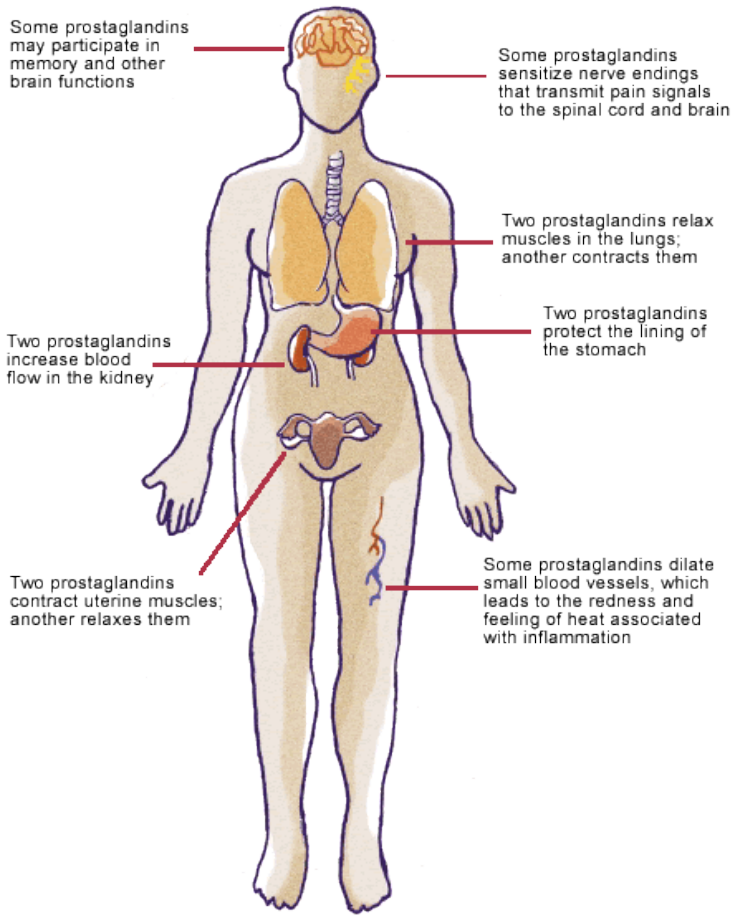
- The organ or tissue involved.
- The receptor to which they attach.
- The bodily function or physiological situation.

Prostaglandins can influence:

- Blood clot formation at the site of an injury.
- Blood flow.
- Healing.
- Inflammation.
- Pain perception.
- Acid secretion in your stomach.
- Smooth muscle in your gastrointestinal (GI) tract.
- Labour induction in pregnancy.
- Menstruation.
- Ovulation.

How are Prostaglandins different from hormones?

Prostaglandins are different from hormones because your endocrine system glands don't release them into your bloodstream like they do hormones. Instead, your tissues make prostaglandins at the site of the action, damage or infection. Prostaglandins have a short half-life and have a short duration of action. Because of this, they can only affect cells that are close by.



Prostaglandin effects on the body

As an example, if you cut your finger, prostaglandins would play a part in your body's response in the following ways:

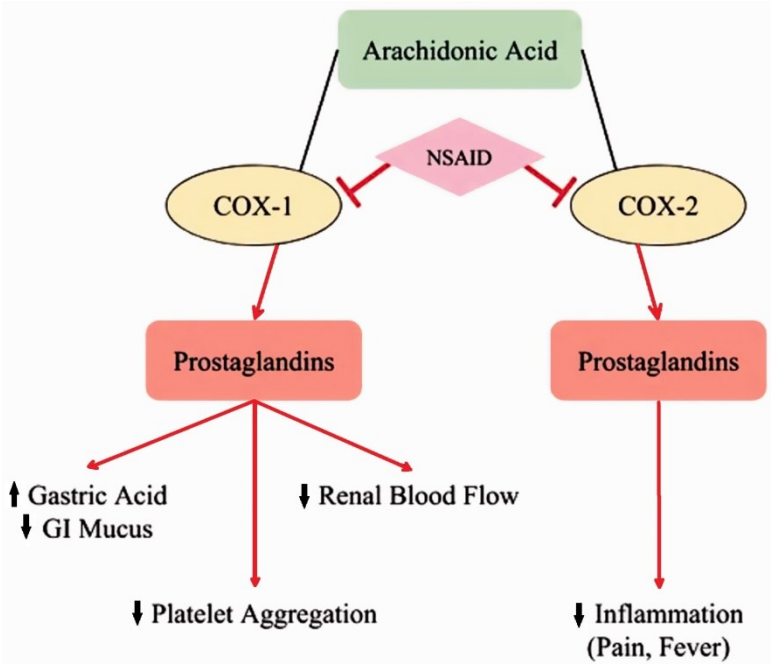
- The affected tissue in your finger would release prostaglandins that signal the platelets in your blood to stick together to form a blood clot at the site of the injury in order to stop the bleeding.
- The affected tissue would release prostaglandins to narrow affected blood vessels to try to lessen blood loss.
- Later the affected tissue would release prostaglandins that trigger the inflammatory response, causing blood vessels to leak fluid into the tissues (swelling). This helps isolate any foreign substances that entered through your broken skin from further contact with your body's tissues. Prostaglandins involved with inflammation also attract white blood cells called phagocytes that "eat" germs and dead or damaged cells.
- Once your injury is healed, the affected tissue will release prostaglandins to break up the blood clot and remove it since it's no longer needed.

As you can see prostaglandins can trigger opposite responses at different times i.e. vessel contraction followed by vessel relaxation later in the healing process.

How Do NSAIDs Help Relieve Pain?

NSAIDs work on a chemical level. They inhibit enzymes, specifically the cyclo-oxygenase-1 **(COX-1)** and cyclo-oxygenase-2 **(COX-2)** enzymes. These enzymes play a key role in making prostaglandins. By blocking the Cox enzymes, NSAIDs stop your body from making as many prostaglandins. This results in NSAIDs have three major therapeutic actions:

- analgesic (pain relief)
- antipyretic (temperature reduction)
- anti-inflammatory (reduce tissue inflammation)



NSAID pathway

What is the difference between Cox-1 and Cox-2?

COX-1 produces prostaglandins that could be thought of as having **a housekeeping function** on the body, such as:

- Platelet aggregation, i.e. preventing blood clot formation
- Increasing mucus secretion to protect the stomach
- control of renal haemodynamics and glomerular filtration rate (GFR)

COX-2 is produced **in response to inflammation** and produce prostaglandins which:

- Cause vasodilatation, enabling the body to flood the affected area with the various substances and cells that remove damaged tissue and are needed to heal the injury
- Increase the effects of bradykinin and histamine, which together cause a further increase in vasodilatation
- Sensitise the afferent C fibres to the effects of bradykinin and histamine, which, in turn, causes pain

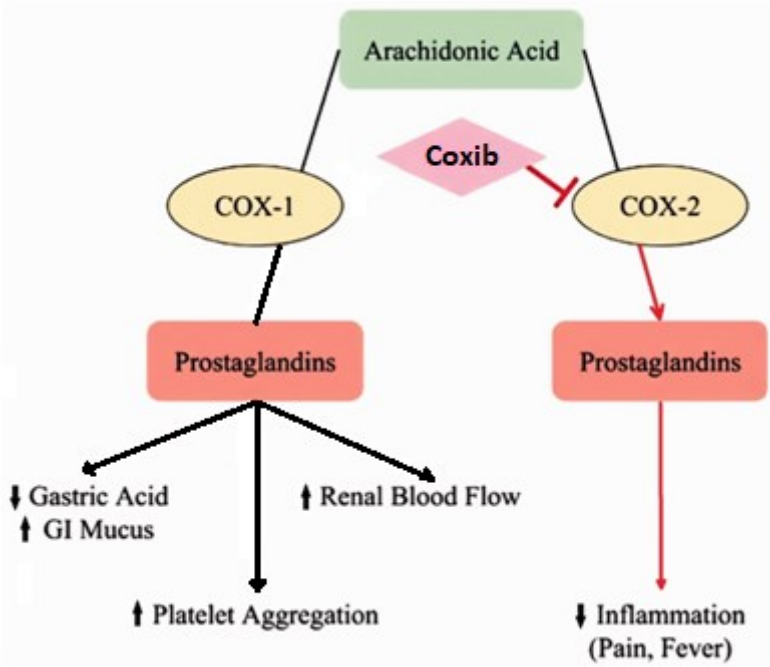
NSAID or Coxib, what is the difference?

Most older 'non-selective' NSAIDs block both Cox-1 and Cox-2 enzymes. COX-2 inhibitors, or coxibs, were developed to specifically block only the COX-2 enzyme and not Cox-1. It was expected that by doing this, the harmful gastric side-effects that come from 'non-selective' NSAIDs would be eliminated, or at least reduced, while still giving the patient good pain relief.

The first coxibs, were launched in the late 1990s and endorsed in 2001 by NICE for use in patients who may be at risk of gastrointestinal side-effects. Unfortunately, in 2004, evidence emerged that indicated that this class of drugs was associated with a higher than expected incidence of cardiovascular side-effects.

Since then, further evidence indicates that many of the non-specific NSAIDs are also associated with a high incidence of cardiovascular side-effects.

Note: Aspirin which is a NSAID, has some benefits that other NSAIDs do not. The biggest is that aspirin works against the formation of blood clots. As a result, you are less likely to form the clots that can cause heart attacks and strokes. Other NSAIDs do not have this effect.



Coxib pathway

What about paracetamol?

Paracetamol (acetaminophen for Americans) is generally not considered an NSAID as it has only minor anti-inflammatory activity and works through a different pathway.

Although paracetamol was discovered nearly 150 years ago and has been used for more than 50 years, the exact way it works is still not fully understood. What is agreed is that paracetamol has a different mode of action to other analgesics. Paracetamol is covered in a separate module.

What Are the Side Effects from Standard NSAIDs?

Most people who use NSAIDs don't have any serious problems with them. But in some, especially those who need pain relief regularly, there can be a downside.

When you take a NSAID it has systemic affects for the whole body, not just the part that hurts. So while an NSAID may do a great job of easing pain, it may also be having other effects, some of them unwanted, in other parts of the body.

Gastric

Gastric ulcers are the side-effect most commonly associated with NSAIDs.

Gastric ulcers do not only occur because the tablet or capsule has an effect on the gastric mucosa while it remains in the stomach. NSAIDs also cause a systemic effect on gastric mucous production, so gastric side-effects also occur with rectal or parenteral (IV/IM) administration. At best, the small amount of drug absorbed by the topical route does mean that this route is associated with fewer systemic side-effects.

Gastric side-effects are a result of systemic, not local, action.

Gastric side-effects range in severity from mild nausea and discomfort, to bleeding gastric ulcers.

The gastric mucus layer prevents gastric acid attacking the stomach wall. Although prostaglandins inhibit the secretion of gastric acid, they also encourage the formation of mucus in the stomach. Because NSAIDs reduce the production of prostaglandins, the normally effective barrier to gastric acid is reduced, which can result in the common side-effects of nausea and discomfort, with the potential for the development of gastric ulceration.

A recent meta-analysis has shown that both the traditional NSAIDs and the newer COX-2 inhibitors increase the risk of gastric side-effects, though COX-2 inhibitors have a lesser effect.

The general advice is to always use the smallest dose possible for the shortest length of time. If a patient is at risk of gastric side-effects, then appropriate gastric protection should also be prescribed. However, NSAIDs and COX-2 inhibitors should be avoided in patients with a history of gastrointestinal disease.

Renal

Prostaglandins are associated with regulating renal blood flow. NSAIDs reduce the blood flow to the kidneys, which makes them work more slowly. However, this is reversible if the drugs are stopped.

They can also be associated with fluid and electrolyte retention, which can worsen other conditions such as hypertension and heart failure. If NSAIDs are taken in high doses, the reduced blood flow can permanently damage your kidneys. It can eventually lead to kidney failure and require dialysis.

International consensus guidelines recommend avoiding NSAIDs in people with eGFR <30, and to avoid prolonged use in those with eGFR 30–59.

Asthma

Approximately 20% of adults with asthma have sensitivity to aspirin. There is cross-reactivity with other NSAIDs and so these drugs should be avoided in sensitive patients.

Careful history taking is needed because, sometimes, patients may not associate over-the-counter remedies that they have taken, such as ibuprofen, with their worsening asthma. Patients with co-existing chronic rhinitis and nasal polyps see to be most at risk.

Platelet effects

Aspirin specifically, has an irreversible effect on platelets. It reduces platelet aggregation and clot formation. Its effect lasts for approximately 7-10 days after stopping the drug, which is the remaining lifespan of the affected platelets, hence the need to stop it about a week before surgery. The risks of stopping or continuing aspirin preoperatively should be considered on an individual patient basis. There may also be a need to stop other NSAIDs a day or two preoperatively. You should check your local guidance.

This effect is why aspirin is prescribed to certain groups of patients to prevent occurrence of complications such as myocardial infarction, strokes and transient ischaemic attacks (TIA).

It has become more apparent recently that NSAIDs antagonise the effect of aspirin, whereas COX-2 inhibitors appear not to.

Cardiovascular

In 2004, it became apparent that the COX-2 inhibitors were associated with an increased risk of cardiovascular events, including death. Subsequent to this, researchers reviewed the safety data on all NSAIDs and found that most of these drugs carry a risk of cardiovascular side-effects, in particular thrombotic effects, such as myocardial infarction and stroke.

A report by the MHRA (UK)* in 2010 describes the cardiovascular risk associated with these drugs, not only in patients who are at high risk, but also all other patients. This report shows that diclofenac carried a similar risk to the COX-2 inhibitors, as did high-dose ibuprofen. On the other hand low-dose ibuprofen and naproxen did not seem to carry the same risk. The current MHRA recommendations are that naproxen would be the drug of choice for patients at risk of cardiovascular events.

NSAIDs are also associated with an increase in blood pressure, and should therefore be used with caution in hypertensive patients.

*(https://www.gov.uk/government/publications/cox-2-selective-inhibitors-and-non-steroidal-anti-inflammatory-drugs-nsaids-cardiovascular-safety/cox-2-selective-inhibitors-and-non-steroidal-anti-inflammatory-drugs-nsaids-cardiovascular-safety)

Routes of Administration - Formulations Available

The most common route of administration is the oral route. However, these drugs can be given by a wide range of routes including oral, parenteral, rectal and topical.

There are relatively few NSAIDs available that can be administered parenterally (IV,IM,subcut) the BNF lists just four:

- Diclofenac
- Ketorolac
- Tenoxicam
- Parecoxib (Coxib)

Each of these can be administered either intravenously (IV) or intramuscularly (IM). However, they are licensed to be used for only a few days (2 or 3 at most), which can limit their usefulness. Examples include Diclofenac, i.e. Voltarol® 75 mg/3 ml, for a maximum of 2 days.

There are often specific administration instructions, e.g. IM diclofenac must be given by deep IM injection, into the gluteal muscle.

Types of Pain Treated by NSAIDs

- Musculoskeletal
- Musculoskeletal indications include:
- Osteoarthritis
- Rheumatoid arthritis
- Ankylosing spondylitis

NSAIDs and COX-2 inhibitors reduce the pain and inflammation associated with these conditions but do not affect the progression of the disease.

For this reason, they are now not as commonly used in rheumatoid arthritis. Other groups of drugs, known as disease-modifying anti-rheumatic drugs (DMARDs), prevent or slow down disease progression, and these tend to be used in preference. However, the NSAIDs and COX-2 inhibitors are still useful for reducing pain, particularly during flare-ups.

In osteoarthritis, paracetamol and topical NSAIDs are preferred where possible, because of the side-effects associated with NSAIDs and COX-2 inhibitors. Topical NSAIDs probably have some additional action as a result of massaging in the preparation.

Dysmenorrhoea

Dysmenorrhoea occurs at the beginning of menstruation when the uterus starts to contract frequently, resulting in pain and cramps. Primary dysmenorrhoea is associated with high levels of prostaglandins, which are responsible for the uterine contraction. This prostaglandin release is blocked by NSAIDs resulting in a reduction in pain and cramping.

Dental

NSAIDs not only have an analgesic effect, but also reduce the inflammation associated with dental procedures such as tooth extraction.

Gout

NSAIDs and COX-2 inhibitors effectively treat flare-ups of acute gout, reducing both the pain and the inflammation. They are also useful when treatment to reduce uric acid levels is initiated, as this can cause an acute gout attack.

Postoperative

By using a combination of analgesic agents, including NSAIDs and COX-2 inhibitors, a patient can receive good levels of postoperative pain relief without needing large quantities of opioids, such as morphine. Consequently the risks of opioid side-effects, such as respiratory depression, are reduced.

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