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"NON-STEROIDAL ANTI-INFLAMMATORY DRUGS"

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Abstract:

Non-steroidal anti-inflammatory drugs (NSAID are members of a therapeutic drug class which reduces pain, decreases inflammation, decreases fever and prevents blood clots. Side effects depend on the specific drug, its dose and duration of use, but largely include an increased risk of gastrointestinal ulcers and bleeds, heart attack, and kidney disease. The term *non-steroidal*, common from around 1960, distinguishes these drugs from corticosteroids, another class of anti-inflammatory drugs, which during the 1950s had acquired a bad reputation due to overuse and side-effect problems after their initial introduction in 1948.

NSAIDs work by inhibiting the activity of cyclooxygenase enzymes (the COX-1 and COX-2 isoenzymes). In cells, these enzymes are involved in the synthesis of key biological mediators, namely prostaglandins, which are involved in inflammation, and thromboxanes, which are involved in blood clotting.

There are two general types of NSAIDs available: non-selective, and COX-2 selective. Most NSAIDs are non-selective, and inhibit the activity of both COX-1 and COX-2. These NSAIDs, while reducing inflammation, also inhibit platelet aggregation and increase the risk of gastrointestinal ulcers and bleeds.

The most prominent NSAIDs are aspirin, ibuprofen, and naproxen; all available over the counter (OTC) in most countries. Paracetamol (acetaminophen) is generally not considered an NSAID because it has only minor anti-inflammatory activity. Paracetamol treats pain mainly by blocking COX-2 and inhibiting endocannabinoid reuptake almost exclusively within the brain, and only minimally in the rest of the body.

Keywords:

NSAID, Pain, OTC etc..

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain.

Some drugs in this class 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.

Recent work has revealed that the side-effect profile of NSAIDs is significant, particularly within the cardiovascular system. Therefore, to use these drugs safely, clinicians must be aware of the clinical status of the patient when prescribing these drugs.

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

Prostaglandin Biosynthesis (The Arachidonic Acid Pathway)[1]

To understand how NSAIDs work and how some of the side-effects occur, it is necessary to look at what eicosanoids do and how they are made in the body.

Eicosanoids are a group of chemical mediators that exert control over some of the body's systems, particularly the inflammation control and immunity systems.

Eicosanoids are derived from arachidonic acid, which is generated from essential fatty acids in the diet.

There are three main groups of eicosanoids and they are all generated by enzyme action

Group	**By the action of**
Prostaglandins	Cyclo-oxygenase
Thromboxanes	Cyclo-oxygenase
Leukotrienes	Various lipoxygenases

This article focuses on the prostaglandin group of eicosanoids, which are formed by the action of cyclo-oxygenase, because their action results in inflammation and enhanced pain sensation, which is blocked by the action of NSAIDs.

There are two forms of the cyclo-oxygenase enzyme (COX):

- COX 1, which is present in most cells most of the time
- COX 2, which is produced largely as a result of inflammation

COX and Prostaglandins [2]

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

- Platelet aggregation, i.e. preventing blood clot formation
- Increasing mucus secretion, to protect the stomach
- Vasodilatation, to heal injury

However, the various prostaglandins have different actions, which may counteract the actions of other prostaglandins. To add to the confusion, there are a number of different prostanoid receptors that they act on, and one prostaglandin may have different actions depending on which receptor it is acting on. There are certain range of actions of prostaglandins produced by COX 1 . The body automatically controls this range of functions by altering the production of these various mediators.

COX-2 is produced in response to inflammation. It activates the mediators PGE_2 and PGI_2, 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

Sensitize the afferent C fibres to the effects of bradykinin and histamine, which, in turn, causes pain

Following table shows the range of actions of some important eicosanoids produced by COX-1

Area of action	**Action**	**Product**
Blood vessels	Vasodilatation	PGD_2 PGI_2 PGE_2
	Vasoconstriction	Thromboxane A_2
Platelet aggregation	Inhibition	PGD_2 PGI_2
	Promotion	Thromboxane A_2
Lungs	Bronchodilatation	PGE_2
	Bronchoconstriction	Thromboxane A_2
Gastrointestinal tract	Relaxation of muscle	PGD_2 PGE_2 (on EP_2 receptor)
	Contraction of muscle	PGE_2 (on EP_1 and EP_3 receptors)
	Inhibition of gastric acid secretion Increase of gastric mucus secretion	PGE_2
Renal	Renin release	PGI_2
	Vasoconstriction	Thromboxane A_2

Theory behind the mechanism of action of NSAIDs[3]

Knowing how prostaglandins are produced and the effects that they have makes it possible to predict that, when NSAIDs block the COX enzymes, they prevent the

formation of prostaglandins and invoke the consequences that result from that.

Usually, blocking COX-1 is a reversible action, whereas blocking COX-2 is often irreversible. However, aspirin is slightly different in action because it irreversibly blocks the COX enzymes by a process called acetylation.

When COX-2 blocks the production of PGE_2 and PGI_2, inflammation and sensitization of the afferent C fibres is reduced. While reducing inflammation alone can reduce pain, it can also reduce pressure on nerves, which may have caused further pain.

Because older, traditional NSAIDs block both COX-1 and COX-2 enzymes, they are termed 'non-selective'. However, the effect on each enzyme may not be equal, with some NSAIDs being more selective for COX-1 or COX-2. This selectivity is influenced by the structure of the COX-2 enzyme, which has a 'side pocket' that can accommodate large bulky molecules, better than COX-1, which does not have the same pocket design.

COX-2 Inhibitors

COX-2 inhibitor medications, or coxibs, were developed to specifically block the COX-2 enzyme. It was expected that by doing this, the harmful gastric side-effects would be eliminated, or at least reduced, while still giving the patient good pain relief.

Side-effects : on different systems [4]

- Gastric
- Renal
- Asthma
- Platelet effects
- Cardiovascular

Gastric [5]

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

The mucus layer prevents gastric acid attacking the stomach wall. Although PGE_2 inhibits the secretion of gastric acid, it also encourages the formation of mucus in the stomach. Because NSAIDs reduce the production of PGE_2, 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 COX-2 inhibitors increase the risk of gastric side-effects, though COX-2 inhibitors have a lesser effect. A review paper estimated that the risk, for low-risk patients per 10 000 patient years for symptomatic ulcers, ranges from 30, for COX-2 inhibitors, to >100, for naproxen, . This compares to a baseline of <10 for the general population

who are not taking NSAIDs. The elderly are at greater risk .

The British National Formulary (BNF) gives examples of the drugs that carry the highest risk :

- Ketoprofen and ketorolac, highest risk
- Piroxicam, intermediate risk, e.g. indomethacin and diclofenac
- Ibuprofen, low risk, up to 1200 mg daily

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 [6]

PGI_2 and PGE_2 are both associated with regulating renal blood flow.

In susceptible individuals, inhibiting the production of these two prostaglandins can result in renal impairment. 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.

Asthma (Respiratory) [7, 8]

Approximately 20% of adults with asthma have sensitivity to aspirin [10].

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.

Platelet effects [9]

Aspirin 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 used in 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 antagonize the effect of aspirin, whereas COX-2 inhibitors appear not to.

Cardiovascular [10]

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 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.

Routes of Administration [11]

The most common route of administration is the oral route. However, these drugs can be given by a wide range of routes:

- Oral
- Parenteral
- Rectal
- Topical

Oral preparations are available in the following forms:

- Tablet
- Capsule
- Soluble tablet
- Orodispersible tablet
- Liquid preparations
- Sustained-release

Tablet

This is the preparation that nearly everyone is familiar with. They are made by compressing powder or granules of the drug together to form the tablet. They may then have a coating added, such as a sugar or a film coating. These coatings serve a number of purposes:

- To help to identify the tablet, e.g. for ibuprofen you may think automatically of a pink tablet because the original Brufen had a pink sugar coating
- To prevent a tablet from disintegrating
- To mask an unpleasant taste
- Enteric coating : It is a slightly different type of coating, which delays breakdown of the tablet so the stomach is not exposed to the drug. This specialized coating protects the drug from stomach acid and only dissolves when the pH of the surrounding fluid rises. An example is diclofenac enteric-coated (e/c) tablets.

All tablets, regardless of the type of coating, need to disintegrate before the drug can be absorbed.

Capsule

- Capsules contain the drug powder or granules within a gelatin shell. This shell can be either hard or soft, although for NSAIDs the most likely is a hard shell, e.g. celecoxib.
- Soft gelatin capsules can also contain liquids, e.g. cod-liver oil capsules.
- Gelatin is an animal product, so may not be acceptable to all patients.

Soluble tablet

Soluble tablets can be useful for patients who struggle to swallow tablets or capsules. They are less suitable for children because the dose they contain is usually an adult dose.

The tablet may contain high levels of sodium. Examples include piroxicam and diclofenac.

Oro dispersible tablet

Oro dispersibles are a relatively new type of preparation, but are becoming more popular. The drug is contained in a freeze-dried film and dissolves very easily in a little saliva, or water. Ibuprofen is available in this formulation.

Liquid preparations

Liquid preparations are usually developed to enable children to take the drug.

They must be clear, they are either syrups or solutions, or cloudy, i.e. suspensions. It is important with liquid preparations is that, the dose must be measured carefully using the appropriate measure, such as an oral syringe or 5 ml spoon.

The most well-known preparation is likely to be ibuprofen, which is widely used for children, however, other drugs, such as nabumetone and mefenamic acid, are also available as suspensions.

Sustained-release

Some preparations, tablets or capsules mainly, are described as sustained-release or modified-release. This enables the patient to take drugs once or twice a day that normally they would have to take several times a day, which is far more convenient. Examples would be Indomethacin and Diclofenac.

Parenteral

There are relatively few NSAIDs available that can be administered parenterally :

- Diclofenac
- Ketorolac
- Tenoxicam
- Parecoxib

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.

There are often specific administration instructions, e.g. IM Diclofenac must be given by deep IM injection, into the gluteal muscle, which should be kept in mind when using these drugs.

As a group of drugs they are not highly water soluble, so excipients may be included, e.g. ethanol or ethylene glycol.

Examples include Diclofenac, i.e. Voltarol7 5 mg/3 ml or Dyloject 75 mg/2 ml, for a maximum of 2 days.

Rectal

It can be very useful as an option when a patient is unable to take a drug by mouth and to avoid the parenteral route.

There is a small range of drugs available by this route, e.g. Diclofenac ,Indomethacin and Ketoprofen.

Topical

Topical preparations may be administered:

- To the skin
- To the eye
- To the skin

Topical treatment can be useful for musculoskeletal pain such as osteoarthritis. A relatively small amount of drug is absorbed through the skin, so, in theory, should cause less of a problem than drugs given systemically.

A range of formulations is available, such as:

- Gels, e.g. ketoprofen and piroxicam
- Patches, e.g. Voltarol
- Sprays, e.g. Traxam and Mobigel

To the eye

NSAID eye drops, such as ketorolac and flurbiprofen, are used after eye surgery to reduce pain and inflammation.

Types of Pain Treated by NSAIDs [12]

- Musculoskeletal
- Dysmenorrhoea
- Dental
- Acute gout
- Postoperative

In all of these cases the use is short term to minimize the risk of side-effects.

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.

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 contractions. 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.

key points to remember

- When an injury occurs, the body produces prostaglandins that are responsible for enhancing the inflammatory response and sensitizing the afferent C fibres
- NSAIDs work by inhibiting the action of COX and stopping the production of prostaglandins
- NSAIDs inhibit the production of prostaglandins that are responsible for a range of actions, including gastric protection, leading to many of the side-effects that are seen with these drugs
- NSAIDs are effective in treating pain that is associated with inflammation and, in particular, musculoskeletal pain.

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