

Novel NSAIDs

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Summary

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most commonly used drugs to relieve a multitude of pain symptoms.² They are readily available and used extensively. There is a lot of concern about their adverse side effects namely cardiovascular (CV) and gastrointestinal (GI) side effects. It is important to have a good grasp of the pharmacology of these drugs in order to use them safely and effectively. NSAIDs work by inhibiting the cyclooxygenase (COX) enzyme system responsible for production of prostaglandins. Prostaglandins mediate pain inflammation and temperature regulation in the body. NSAIDs can be divided into selective and non-selective types. Three isoforms of COX have been identified COX-1, COX-2 and COX-3. Selective NSAIDs act on these isoforms. COX-1 is anti-inflammatory, COX-2 pro-inflammatory and COX-3, a variant of COX-1, does not produce prostaglandins. The CV side effects of these drugs can be wide ranging and include a rise in blood pressure (BP) and a higher risk of thromboembolic events. Patients also suffer from peptic ulcer disease or bleeding in the stomach as a result of their use. NSAIDs can cause liver and kidney toxicity and should be used with caution in patients with bleeding tendencies. New NSAIDs on the market include; lornoxicam (xefo[®]), meloxicam (coxflam[®]), celecoxib (celebrex[®]), parecoxib (rayzon[®]) and etoricoxib (arcoxia[®]). New ways of delivering NSAIDs to the body with minimal or no side effects are being researched. Novel technology in this field includes nano formulated NSAIDs; indomethacin (tivorbex[®]) and diclofenac (zorzolex), prodrugs and multi action drugs; cyclooxygenase inhibiting nitric oxide donors and hydrogen sulphide releasing drugs. Further exciting innovations are in the pipeline that could change the face of how we use these drugs. Until then they must be used with careful consideration and only if the benefits of use outweigh the risks.

Keywords: preoperative anxiety, music medicine, music intervention, gynaecological patients

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most commonly used drugs^{1,2} in adults to relieve a multitude of pain symptoms.³ A variety of NSAIDs are available on the market and because they are readily available and used extensively across the population, it is important to have a good grasp of the pharmacology of these drugs. In as much as NSAIDs have become useful anti-inflammatory drugs, there is a lot of concern about their adverse side effects namely cardiovascular (CV), gastrointestinal (GI), renal and asthma triggering side effects.^{3,5,6} This article is a brief overview of the history of NSAIDs with specific reference to novel NSAIDs on the market influencing current anaesthetic practice.

How do they work?

The cyclooxygenase (COX) enzyme system is used in the production of prostaglandins from fatty acids.⁴ Membrane phospholipids are released from cell membranes for a variety of reasons, mainly cell damage. These phospholipids are converted into arachidonic acid by phospholipase A₂.⁴ Arachidonic acid is converted into leukotrienes by lipoxygenase (LOX) and is also converted by COX into prostaglandin G₂ (PGG₂).⁴ PGG₂ is converted into prostaglandin H₂ (PGH₂) and PGH₂ is converted into five active forms of prostaglandin; prostaglandin D₂, prostaglandin E₂, prostaglandin F_{2α}, prostacyclin and thromboxane A₂.^{4,7,9} Prostaglandins are mediators in pain, inflammation, temperature

regulation, mitosis and neuromuscular functions.⁴ NSAIDs inhibit this system at various levels in the production line. The result of this inhibition is that there is a decrease in pain, inflammation and fever.¹⁰

COX enzymes

COX has three known isoforms but two of them have current clinical use.^{4,5} It is hypothesised that COX-1 mediates anti-inflammatory processes and COX-2 pro-inflammatory processes.⁶ Traditional NSAIDs block all COX pathways.^{4,5}

We now know that

COX-1 is found in most tissue types and mediates cellular homeostasis functions such as, protection of gastric mucosa, regulation of renal blood flow and platelet aggregation.⁵

COX-2 is found in the brain, spinal cord and kidneys and its production is easily stimulated by inflammatory conditions in response to cytokines (interferon, TNF and IL-1), hormones, growth factors, hypoxia and it can be found in tumour endothelium.⁹

COX-3 a variant of COX-1 does not produce prostaglandins and is expressed in the cerebral cortex and in the heart.⁵

We have two main types of NSAIDs, selective (traditional) and non-selective (coxibs).⁵ This refers to the ability of a NSAID to

inhibit COX enzymes. Non-selective NSAIDs inhibit both COX-1 and COX-2 and selective NSAIDs inhibit COX-2 more than COX-1.⁴ Research has shown that the beneficial effects of NSAIDs come from their ability to block COX-2 and their adverse side effects are largely due to inhibition of COX-1.⁴ Therefore drugs that selectively inhibit COX-2 are of a greater advantage.

In 1999, GD Searle and Pfizer (Pfizer) came out with the first COX-2 inhibitor celecoxib (celebrex®).⁷ Merck released rofecoxib (vioxx®) soon after this.⁷ These two drugs showed initial exponential success and grossed millions of dollars for their companies.⁷ Two trials the Celecoxib Long-term Arthritis Safety Study (CLASS) and Vioxx Gastrointestinal Outcomes Research (VIGOR) supported the use of these drugs as they have effective inflammatory properties with less of the GI effects.⁵

Rofecoxib and valdecoxib were taken off the market in 2004 due to mounting evidence of increased risk of heart attack and stroke.^{5,7} Celecoxib was allowed to remain on the market, however with a black box warning that there was a risk of adverse cardiovascular events as evidenced by Adenoma Prevention with Celecoxib (APC) trial and the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial.^{5,7} Manufacturers of NSAIDs were forced to make labelling changes to their products highlighting the cardiovascular adverse events.⁷ The dilemma is finding a balance between side effects of COX-2 inhibitors versus the side effects of non-selective inhibitors.

What are these side effects?

The CV effects can be wide ranging and include accelerated atherosclerosis and a rise in blood pressure; COX-2 inhibition can worsen outcomes in patients with ischaemic heart disease and cause larger infarcts, myocardial wall thinning and rupture post myocardial infarct.^{5,7} There is a higher risk of thromboembolic events in patients with cardiovascular disease or risk factors for disease, as well as increased risk of arrhythmias and heart failure.⁵

GI effects depend on the duration of use. Short term effects are mainly dyspepsia and discomfort whereas long term high dose usage of NSAIDs can lead to peptic ulcer disease and bleeding from the stomach.^{5,11}

NSAIDs can also cause liver toxicity resulting in the inability to metabolise paracetamol efficiently and more adversely, liver dysfunction and failure.⁵

Even if used for a short period of time, NSAIDs can cause renal toxicity and therefore should be used with caution in patients with underlying renal disease.⁵ They disturb fluid and electrolyte control, diuresis, blood flow and perfusion to the kidney, and specifically COX-2 inhibition can increase serum potassium.⁵ However, small doses of NSAIDs are usually safe for the kidney.⁴

Generalised bruising and bleeding can result, especially in patients on antithrombotic treatment who show an increased risk of bleeding when using NSAIDs.¹²

Patients who are sensitive to NSAIDs may find that they have an exacerbation of their asthma after using them.⁴

Who should avoid NSAIDs?

An anaesthetic practitioner must always be cautious when using NSAIDs and perhaps avoid their use in high risk patients with uncontrolled hypertension, cardiovascular disease, ulcer disease and bleeding tendencies.⁵ Risk factors for GI problems include age over 60 years, history of peptic ulcer disease or GI bleeding, history of CV disease and using other drugs or having serious comorbidities.¹¹ Every case must be considered on its own merit.

Remember: COX-2 selective inhibitors produce more adverse CV effects and non-selective COX inhibitors have more GI effects.

With the above as background, we can now discuss some of the newer drugs on the market in use.

New NSAIDs on the market

1. Lornoxicam (Xefo®)⁸ is a non-selective COX inhibitor. It is available in oral (4 mg and 8 mg film coated tablet and 8 mg rapid, film coated tablet) and parenteral formulations (8 mg powder for injection). The dose is 8–16 mg per day in 2 to 3 divided doses, in renal patients the maximum dose is reduced to 12 mg. Its bioavailability is 90–100%, protein binding is 99%. It is metabolised by CYP2C9 in the liver. The elimination half-life is 3–4 hours. Xefo® is excreted 2/3 by the liver and 1/3 by the kidney. It is not recommended for children under the age of 18 years.

It is used in the treatment of various types of pain especially pain resulting from inflammatory diseases of the joints, osteoarthritis (OA), post-surgery and sciatica and is an adjunct to opioids.

Side effects include nausea and diarrhoea, headache, bronchospasm and Stevens–Johnson syndrome.

As with other NSAIDs, it is not recommended for pregnant and breastfeeding women.

2. Meloxicam (Coxflam, Flexocam, Loxiflam, Melflam, Mobic®)⁸ is a COX-2 selective NSAID. It is available in oral and parenteral formulations. The dose is 7.5 mg orally 12-hourly up to a maximum of 15 mg/day. Its bioavailability is 89% and protein binding is 99.4%. It is metabolised by the liver CYP2C9 and 3A4 systems. The elimination half-life is 20 hours. Meloxicam is excreted in urine and faeces. It is used for pain and inflammation in rheumatoid arthritis (RA) and OA. The side effects of using it include allergic reactions, especially in patients with asthma, new onset or worsening high BP, oedema and reduced kidney function.

3. Celecoxib (Celebrex®)⁸ is a COX-2 specific NSAID that is available as an oral formulation (capsules, 50 mg, 100 mg, 200 mg, 400 mg). The usual dose for acute pain is 400 mg initially, then 200 mg 12-hourly as required. Protein binding is 97%. Metabolism takes place in the liver by the CYP2C9 system. The elimination half-life of Celebrex® is 7.8–13 hours

depending on hepatic impairment. Excretion is 57% in the faeces and 27% in the urine. Celebrex[®] is used in the treatment of a variety of painful conditions such as OA, RA, ankylosing spondylitis, acute pain, musculoskeletal pain and painful menstruation. It is also used to reduce polyps in rectum and colon in patients with familial adenomatous polyposis. Side effects can be disabling – abdominal pain, nausea, diarrhoea – and can also include more serious effects such as heart attacks, strokes, GIT perforation, GIT bleeding, kidney failure and anaphylaxis.

4. Parecoxib (Rayzon[®]) is a COX-2 specific NSAID that is available in IV and IM formulations (40 mg). The dose is 40 mg 6–12 hourly, with a maximum 80 mg/day. Bioavailability is 100% and protein binding is 98%. It is metabolised in the liver. The elimination half-life is 22 minutes, excretion is via the kidneys. Rayzon[®] is used for short term peri-operative pain control and also as an adjunct to opiates. Please note it is not approved by the FDA in the US.

5. Etoricoxib (Arcoxia[®]) is a COX-2 specific NSAID. It is available as an oral formulation (30 mg, 60 mg, 90 mg, 120 mg film coated tablets). The dose in OA is 60 mg daily, in RA 90 mg daily, and in gouty arthritis 120 mg daily. The bioavailability is 100% with protein binding of 92%. It is metabolised in the liver. The elimination half-life is 22 hours. It is excreted by the kidneys. It is not approved for use in the US. The side effects are mainly fixed drug eruptions, generalised erythema, and erythema multiforme-like eruptions.

The current problem

The world has an ageing population and there is an increasing use of NSAIDs in patients with comorbidities.¹¹ These patients therefore face a risk of NSAID toxicity and because of the risk of side effects they may not take their medication adequately.¹¹ Furthermore, musculoskeletal conditions are one of the commonest reasons that patients seek healthcare.⁵ New ways of delivering NSAIDs to the body with minimal or no adverse effects are needed. Scientists are now researching the options.

New technology

Nano formulated NSAIDS

These are low dose micro-ionised NSAIDs. Advanced scientific technology is used to produce submicron sized drug particles which are 10–20 times smaller than their original size.^{2,5} The theory is that an increased drug surface area will enhance dissolution and absorption of the drug with the aim of achieving similar effects to normal NSAIDs with reduced adverse effects.^{2,5}

Currently approved nano formulations by the FDA in the US are indomethacin (tivorbex) and diclofenac (zorvolex) for the treatment of mild to moderate pain.⁵ At lower doses they achieve similar peak plasma levels, shorter time to peak plasma concentration and lower overall systemic effects.⁵

Prodrugs

Prodrugs are drugs that are converted chemically or by enzymatic action in vivo, releasing an active drug in order to get a desired pharmacological effect.² The aim is to remove the negative side effects of a desired drug in the systemic circulation; for example, adding ester groups to NSAIDs containing carboxylic acid groups can reduce GIT irritation and bleeding.²

Multi target drugs

Cyclooxygenase-inhibiting nitric oxide (NO) donors (CINODS/NO-NSAIDs) are a new class of drug in development. They target multiple pathways with one drug.⁵ NO is a potent vasodilator and has protective effects on the GI tract.¹³ It protects the integrity of the gut by stimulating release of bicarbonate and mucus, protects epithelial cells from injury and inhibits the release of inflammatory mediators.⁵ By adding NO to NSAIDs it is hoped that the adverse GI effects will be reduced.

Hydrogen sulphide releasing drugs (H₂S)

Hydrogen sulphide is said to have vasodilatory properties and anti-inflammatory properties.^{3,5,14} It has an important role in gastrointestinal mucosal homeostasis.¹⁵ Early animal studies have shown lower GI and CV toxicity when this compound was used with diclofenac and naproxen than when these drugs were used alone.^{4,5} Drugs containing this compound are still in the preclinical stage of development.^{3,5,14}

Conclusion

NSAIDs are some of the most important drugs we have for pain relief today. Further exciting innovations are in the pipeline that could change the face of how we use them. Until then, they must be used with careful consideration and only if the benefits of use outweigh the risks.

Conflict of interest

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