Update in
Anaesthesia

Non-steroidal Anti-inflammatory Drugs

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Summary

NSAIDs are effective analgesics used almost universally to reduce perioperative and long term pain, especially when associated with inflammatory conditions. The side effects however, are numerous and clinically important, possibly having far greater impact than we imagine. The future may herald tighter regulation of this class of drug.

INTRODUCTION

The description "non-steroidal anti-inflammatory drugs" (NSAIDs) is the term used when referring to a group of drugs that are united by their mode of action (anti-inflammatory) and by virtue of not being steroids. Most are organic acids and conventional NSAIDs can be grouped according to their chemical structure (Table 1). Apart from their anti-inflammatory action, they also have antipyretic and analgesic activity. The latter is particularly useful as this comes without any sedation, effect on respiration in therapeutic doses or the potential for addiction, all normally associated with opioid drugs. Most common NSAIDs can be given orally or rectally and some may be administered intravenously. Most NSAIDs display similarities in their side effect profile.

MECHANISM OF ACTION

Conventional NSAIDs act as non-specific inhibitors of the enzyme cyclo-oxygenase (COX), which is part of the arachidonic acid pathway that leads to the formation of various eicosanoid messenger molecules. Therefore in addition to reducing the synthesis of prostaglandins (PGH_2, PGE_2, PGF_2), the production of leukotrienes, prostacyclins and thromboxanes are also reduced (Figure 1). Prostaglandins (PGs) act locally producing many diverse effects via G-protein coupled membrane receptors and are synthesised in most cells of the body.

The COX enzyme has two distinct isoforms termed COX-1 and COX-2. These two enzymes are coded for by two genes and expressed differentially in various tissues. The COX-1 enzyme is described as being "constitutive" and is expressed continuously in many tissues, for example kidneys, stomach, lung liver and platelets. It is involved in various protective homeostatic mechanisms, for example renal blood flow, gastric mucosal integrity and platelet aggregation. In contrast, the COX-2 enzyme is described as being "inducible", such that it is not normally present in any appreciable quantity in tissues and its production is induced in sites of inflammation and tissue injury by cytokines (e.g. interleukin-1) and tumour necrosis factor alpha. Conventional NSAIDs inhibit both enzymes; inhibition of COX-1 accounting for most of

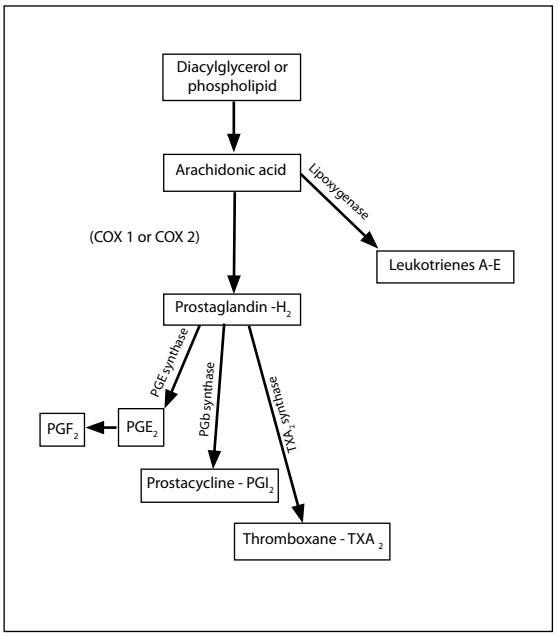

Figure 1. *The prostaglandin pathway*

Table 1. *Classification of NSAIDS*

Conventional NSAIDs – with examples	
Salicylic acid derivatives	Aspirin
Acetic acid derivatives	Diclofenac, Indomethacin
Propionic acid derivatives	Ibuprofen, Naproxen, Ketoprofen
Enolic acid derivatives	Piroxicam, Phenylbutazone
Fenamic acid derivatives	Mefenamic acid
Non-acidic	Nabumetone

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the unwanted side effects of NSAIDs (see below) and inhibition of COX-2 accounting for the therapeutic effects. In theory the 'perfect' NSAID would therefore only inhibit COX-2, leaving COX-1 to continue with normal homeostatic processes. This ideal has recently been achieved to a degree with the introduction of specific COX-2 inhibitors. Currently available drugs in this class are celecoxib, etoricoxib and parecoxib. Rofecoxib (Vioxx) has been withdrawn by the manufacturer because of concerns about the apparent increased risk of adverse cardiovascular events (see below).

This model is an over simplification, with COX-2 probably having a greater role in other physiological processes than previously thought, particularly in female reproduction.

As shown above, the COX enzymes are involved in the production of PGH_2, a precursor of various other PGs that play an important role in the inflammatory process. PGs themselves play little part in the direct production of pain; they cause localised increased blood flow and vascular permeability that leads to swelling and erythema seen at the site of inflammation, while PGE_2 and $PGF_2\alpha$ sensitize peripheral nerve fibres to both mechanical, chemical, thermal stimuli and locally released pain-producing stimuli such as bradykinin, histamine and serotonin. PGs are also released in the CNS where they are thought to be involved in the release of substance-P. This enhances synaptic transmission in the dorsal horns resulting in the hyperalgesia associated with inflammation. Traditionally, NSAIDs were thought to decrease pain by blocking the peripheral effects, but it now believed that they exert at least part of their effect centrally, by reducing prostaglandin levels in the CNS.

Not surprisingly, NSAIDs have been shown to be effective analgesics drugs, particularly against bone pain (e.g. arthritis, fractures) and have a morphine-sparing effect after abdominal,[1] thoracic[2] and orthopaedic surgery.[3] As a consequence patients experience less sedation, improved respiratory function, reduced risk of urinary retention and earlier return to eating and drinking. As a result patients mobilise sooner, and hospital costs are reduced. Consequently, these drugs have found an increasing use in the perioperative phase, in particular ketorolac (non-specific COX inhibitor) and parecoxib (COX-2 inhibitor) as they can be given parenterally.

The other therapeutic role of NSAIDs is the reduction of fever. Body temperature is normally regulated around a set-point by the hypothalamus. Prostaglandins produced in disease states, cause this set-point to be raised, an effect partly negated by NSAIDs.

SIDE EFFECTS

Gastrointestinal tract

The effects of NSAIDs on the gastric mucosa are perhaps the best recognised. Prostaglandins have a 'gastro-protective effect' in that they act to cause a decrease in gastric acid production, an increase in production of the protective gastric mucosal barrier and an increase in local gastric mucosal blood flow. Decreasing prostaglandin production therefore results in damage to the gastric mucosa. NSAIDs may also cause damage to the gastric mucosa by a direct contact physiochemical effect. A combination of both effects can lead to effects ranging from mild epigastric discomfort to gastric erosions associated with upper GI bleeding. There is considerable inter-patient variability in the degree of sensitivity with the elderly being most at risk. COX-2 selective NSAIDs have been shown to be associated with a lower incidence of upper GI side effects.[4]

Platelets and the cardiovascular system

Impaired platelet function (reduced aggregation) is a common effect of all non-selective NSAIDS, as a result of decreased thromboxane A_2 (TXA_2) production. TXA_2 is present in large amounts in activated platelets and acts locally as a chemo-attractant for other platelets, leads to the formation of a platelet plug and induces localised vasoconstriction. Most NSAIDs inhibit COX-1 in a competitive manner and therefore is dependant on the drug concentration in the plasma. Aspirin, however, acts in a non-competitive manner by irreversibly inactivating COX. Platelets cannot synthesise proteins de novo, and are therefore unable to produce "new" COX enzyme, thereby rendering them ineffective for their lifespan of up to ten days. It is for this reason that aspirin must be discontinued for a week prior to elective surgery.

The cardiovascular side effects of NSAID-induced eicosanoid depletion are not simple. PGI_2, produced by normal endothelium, is an inhibitor of platelet aggregation and contributes to the antithrombotic properties of intact blood vessels. Also, in contrast to TXA_2, prostaglandins generally cause vasodilatation of vascular beds and increased blood flow to organs (the exception being the pulmonary vasculature where they cause vasoconstriction). Vascular PGI_2 is COX-2 dependent which might explain the higher risk of cardiovascular side effects seen with some COX-2 selective NSAIDs.

There is new evidence that the use of NSAIDs may lead to an increase in the risk of myocardial infarction (MI) in the general population.[5] This appears to be an effect of most NSAIDs rather than being attributable to certain drugs. A small increase in MI risk is associated with the long-term use of certain NSAIDs (e.g. diclofenac), others confer no apparent increased risk (ibuprofen) or perhaps even slightly reduce the risk (Naproxen).[6] The greatest risk appears to be with the long-term use of COX-2 inhibitors, this has been shown to be associated with an increased risk of myocardial infarction and stroke (CVA). As a result, rofecoxib was withdrawn by the manufacturers and most authorities now recommend that COX-2 specific drugs are not used in preference to non-selective ones, unless they are specifically indicated, and only after a full assessment of the cardiovascular risk.[7] For this reason in countries that have licensed parecoxib and ketorolac, it is only for short-term postoperative pain relief.

Renal

In patients with heart failure, chronic renal failure and/or hypovolaemia, renal blood flow is much more dependent on prostaglandin-induced vasodilatation than it would be in a healthy person. As a result of this, NSAID induced reduction in prostaglandin levels can precipitate acute renal failure. The inhibition of the prostaglandins normally inhibiting anti-diuretic hormone production leads to increased sodium and water retention with the risk of oedema and/or hypertension. Consequently, all NSAIDs are contraindicated in patients with heart failure.

Obstetrics

Prostaglandins are important for initiating labour and NSAID usage can lead to prolonged labour and a NSAID (commonly rectal

indomethacin) is sometimes used as a tocolytic in premature labour. In this context there are potentially serious side effects including foetal oliguria, and premature closure of the ductus arteriosus. Normally patency of the ductus arteriosus is maintained by PGE_2 and NSAID-induced closure in utero can lead to pulmonary hypertension and myocardial infarction. NSAID usage may increase the risk if miscarriage. The effect seems to be greatest if NSAIDs are used for more than a week and around the time of conception.[8]

Hypersensitivity reactions

Hypersensitivity reactions to NSAIDs may manifest as a spectrum from urticaria and rhinitis to bronchospasm, angio-oedema and in extreme cases hypotension and shock. The reactions seen in patients with no history of asthma are thought to be immune mediated, whereas the bronchospasm sometimes seen in asthmatics is not.

The terms aspirin exacerbated respiratory disease (AERD) or aspirin induced asthma (AIA) refer to a worsening of asthma following dosage. A possible mechanism is the build-up of arachidonic acid as a result of COX inhibition, with the result that it is converted to leukotrienes (by lipoxygenase) which acts as a bronchoconstrictor. These individuals are thought to have a discrete disease entity associated with nasal polyps. There is a strong cross reactivity between other NSAIDs, although COX-2 selective NSAIDs appear to be safe.[9] The estimated prevalence of AERD is 3% when based on population studies but around 20% when based on provocation testing but paediatric prevalence is 2% to 5%.

Drug interactions

NSAIDs can interact with other drugs in various ways. Firstly, as a result of their potential effect on renal function the plasma levels of other drugs may be affected (e.g. lithium). Secondly, NSAIDs may compound the effects of another drug. For example, patients taking an NSAID and warfarin are at greater risk of severe haemorrhage as both drugs exert an anti-coagulant effect. Thirdly, NSAIDs can interact pharmacologically with another drug to alter its effect. An example of this is the elevated international normalised ratio (INR) which may occur in patients taking warfarin and a concomitant NSAID.

Miscellaneous

Reyes syndrome is characterised by encephalopathy and fatty degeneration of the liver, usually occurring after a viral like illness. It is more common in children and associated with aspirin ingestion during the early viral part of the illness. Most countries do not recommend the use of aspirin in children under 16 with fever.

FURTHER READING

Goodman and Gilmans's The Pharmacological Basis of Therapeutics, 11th Edition, McGraw Hill. Available at: http://www.jr2.ox.ac.uk/bandolier/booth/painpag/

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