Cyclo-oxygenase-2 inhibitors

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Revalidation FOR ANAESTHETISTS
RCA Revalidation matrix
Matrix reference 1A02

Key points

The enzyme cyclo-oxygenase-2 is an inducible enzyme especially in inflammatory cells.

Cyclo-oxygenase-2 inhibitors demonstrate clinical efficacy for the treatment of acute and chronic painful conditions with an opioid sparing effect.

Cyclo-oxygenase-2 inhibitors have fewer gastrointestinal side-effects when compared with conventional non-steroidal anti-inflammatory drugs.

Concerns about cardiovascular safety led to the market withdrawal of Rofecoxib.

Parecoxib remains a useful analgesic drug in the peri-operative period.

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Non-steroidal anti-inflammatory drugs (NSAIDs) are used by millions of patients for many painful pathological disorders.[1] Studies demonstrate their clinical efficacy in both acute and chronic pain. When compared with placebo, NSAIDs show superior analgesic efficacy across a wide spectrum of conditions including postoperative pain, cancer pain, and musculoskeletal conditions. However, NSAIDs have failed to show any benefit in neuropathic pain. Conventional NSAIDs reversibly inhibit the enzyme cyclo-oxygenase (COX), thereby preventing the production of both prostaglandins and thromboxanes from membrane phospholipids. There are two isoforms of the COX enzyme, COX-1 and COX-2. These isoforms vary in their distribution and expression but are similar in size, substrate specificity, and kinetics.

Conventional NSAIDs inhibit the two isoforms to varying degrees, which can cause adverse effects in the gastrointestinal (GI) tract, kidney, respiratory system, and platelets. These side-effects led to the development of cyclo-oxygenase-2 inhibitors (coxibs).

Coxibs are selective inhibitors of the COX-2 isoenzyme. As the anti-inflammatory effects of conventional NSAIDs were predominantly believed to be mediated by inhibition of COX-2, and their GI side-effects by inhibition of COX-1, it was hypothesized that selective coxibs would provide a safer alternative to conventional NSAIDs.

COX pathway

Prostanoid is the term used to describe a subclass of eicosanoids consisting of the prostaglandins and the thromboxanes. Prostanoids are metabolites of arachidonic acid that are produced via the COX pathway. They are autocrine and paracrine lipid mediators that contribute to inflammatory pain and play important roles in the maintenance of normal physiological function of several organ systems, for example cytoprotection of the gastric mucosa and maintaining normal platelet function. Prostaglandins production requires the conversion of arachidonic acid to the intermediate prostaglandin H_2 catalysed by the COX enzyme (Fig. 1).

COX is the enzyme responsible for the formation of prostanoids. Different tissues express varying levels of COX-1 and COX-2. COX-1 is considered a constitutive enzyme, being found in most mammalian cells and is responsible for the production of prostaglandins. In contrast, COX-2 is almost undetectable in most normal tissues except in the brain, kidney, uterus, and prostate. It is an inducible enzyme, especially in inflammatory cells, including monocytes and macrophages that can be activated by various cytokines. COX-2 has been shown to be up-regulated in various carcinomas and appears to have a role in oncogenesis. Pro-inflammatory triggers such as tissue damage and arthritis cause release of cytokines and other inflammatory mediators that lead to increased production of prostaglandins E2 (PGE2). PGE2 has the greatest impact on processing pain signals by binding to end-plate receptors and amplifying the response of peripheral primary sensory neurons to painful stimuli. Four subtypes of PGE2 receptors, EP1, EP2, EP3, and EP4, have been identified.[2] Decreased firing thresholds and increased membrane excitability result from PGE2 receptor binding and activation that may be demonstrated experimentally. Increased firing of action potentials from sensory nerves leads to greater afferent input to the dorsal horn of the spinal cord, and results in changes in secondary (second-order) sensory neurone function, gene expression, and cell phenotype, termed central nervous system plasticity. The altered states of pain transmission and modulation lead to hyperalgesia (seen as hypersensitivity to painful stimuli around a wound) and allodynia (pain felt as a result of a usually innocuous stimulus, such as pain on walking in arthritis).

COX-2 inhibitors

NSAIDs, among the most frequently used analgesics, reduce production of prostanoids including PGE2 by inhibiting COX-1 and COX-2. Used in the treatment of acute pain for

doi:10.1093/bjaceaccp/mkt004 Advance Access publication 20 February, 2013

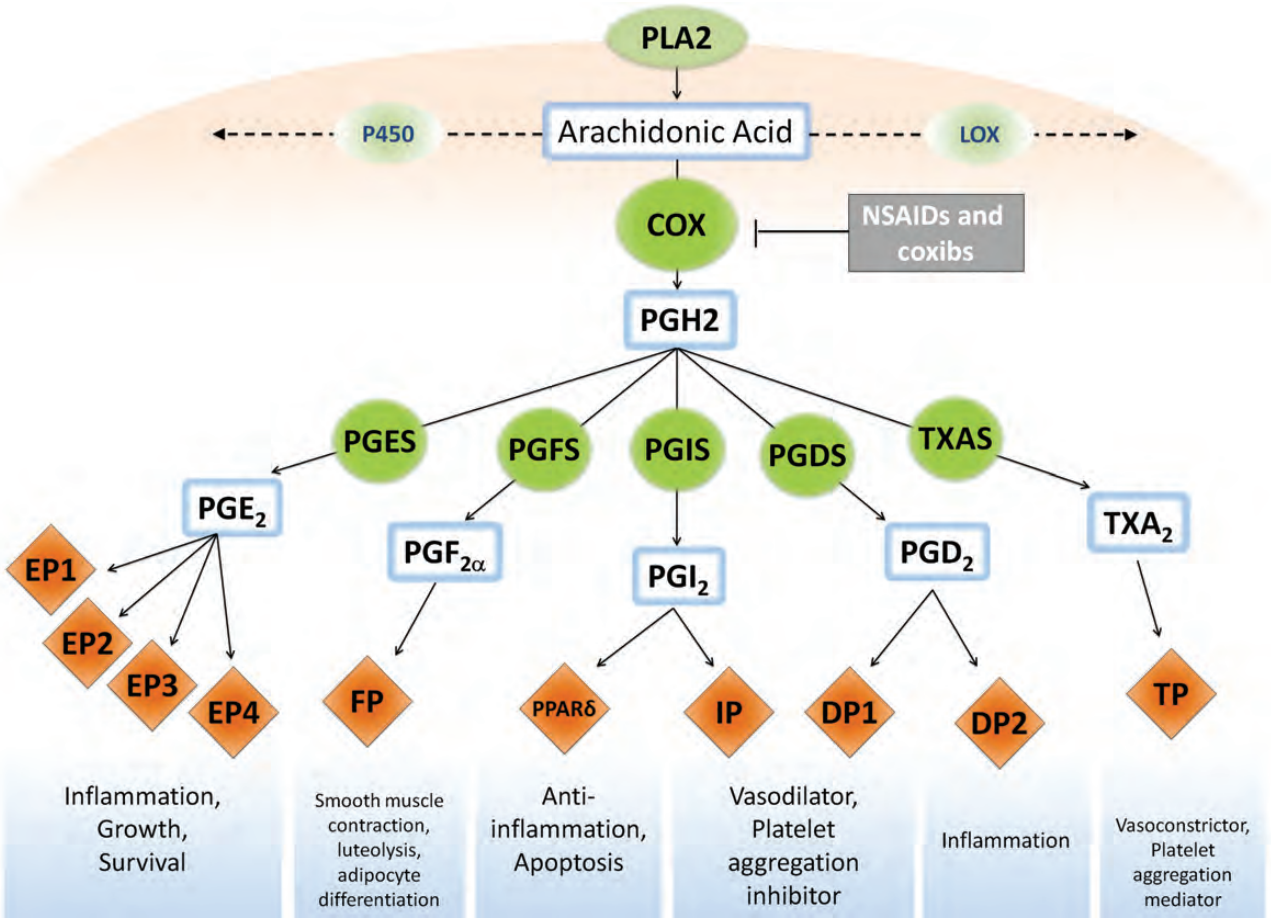

Fig 1 The cyclo-oxygenase (COX) pathway. Arachidonic acid is released from cell membranes by cytoplasmic phospholipase A2 (PLA2). Free arachidonic acid is metabolized to eicosanoids through three major pathways: the COX pathway, the lipoxygenase (LOX) and the cytochrome P450 mono-oxygenase pathways. In the COX pathway, the key step is the enzymatic conversion of arachidonic acid to PGH2 by COX. PGH2 is subsequently metabolised to prostanoids, including prostaglandins (PGs) and thromboxanes (TXs) by specific prostaglandin and thromboxane synthases. Reproduced with kind permission from *Progress in Lipid Research*.[2] ©Elsevier Ltd.

their opioid sparing effects, as part of a multimodal analgesic regimen or, in chronic painful conditions, their place is well established. By inhibiting COX, NSAIDs diminish the effect of the COX up-regulation and could, perhaps, be viewed as anti-hyperalgesic and anti-allodynic rather than analgesic.

The side-effects of NSAIDs are well known and are listed in Box 1.

Box 1 Side-effects of conventional non-steroidal anti-inflammatory drugs

Gastrointestinal (GI) bleeding and ulceration
Thrombotic events such as myocardial infarction and stroke
Renal impairment
Fluid retention
Exacerbation of asthma in NSAID sensitive patients
Inhibition of platelet aggregation and vasoconstriction
Drug interaction (e.g. warfarin and lithium)

Coxibs were developed and introduced to the market to provide anti-inflammatory and analgesic activity similar to that of conventional NSAIDs, but without their upper GI toxicity, which results largely from COX-1 inhibition. The perceived safer therapeutic profile led to several agents being introduced but one should note that all coxibs currently available still have the potential to cause GI side-effects, for example dyspepsia.

Celecoxib (Celebrex®) was the first COX-2 selective inhibitor to be introduced into clinical practice in the 1999 and, together with rofecoxib (Vioxx®) a more potent COX inhibitor, was available as oral preparations. These were widely prescribed throughout the UK and USA for patients with rheumatoid and osteoarthritis and were followed by other oral preparations for example, valdecoxib, etoricoxib, and lumiracoxib. Parecoxib (Dynastat®), a prodrug of valdecoxib, is the only water-soluble coxib and permits parenteral administration, of particular relevance to anaesthetists especially in patients in whom oral administration is restricted. It is used in the treatment of acute rather than chronic pain. Meloxicam warrants specific mention as although it is often classed as a conventional

NSAID at lower doses it has preferential COX-2 inhibition and has been included in systematic reviews evaluating clinical and cost-effectiveness of coxibs.[3]

Celecoxib has been shown to have similar clinical efficacy as conventional NSAIDs when treating osteoarthritis and rheumatoid arthritis and is superior to placebo.[4] Compared with conventional NSAIDs, celecoxib is associated with fewer drug withdrawals for GI complications and complicated upper GI events as well as fewer endoscopic GI ulcers.[3] Celecoxib currently holds a UK license for the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Likewise, rofecoxib was shown to have similar clinical efficacy when compared against conventional NSAIDs when treating osteoarthritis and rheumatoid arthritis. Significantly fewer GI adverse effects and endoscopic ulcers were reported with rofecoxib when compared with conventional NSAIDs. However, it has been withdrawn from the market because of cardiovascular safety concerns. Parecoxib is an active prodrug of valdecoxib (a coxib on its own which has now been voluntarily withdrawn because of concerns about serious skin reactions) and is currently licensed for the short-term management of acute post-operative pain. This contrasts with valdecoxib, which was licensed for use in chronic conditions such as osteoarthritis (Box 2).

Box 2 List of cyclo-oxygenase-2 inhibitors

Celecoxib—available in UK as oral preparation
Etoricoxib—available in UK as oral preparation
Parecoxib—available in UK as i.v./i.m. preparation
Rofecoxib—withdrawn for UK market in 2004
Valdecoxib—withdrawn from UK market in 2005
Lumiracoxib—withdrawn from UK market in 2007

A 2009 Cochrane systematic review of seven studies found that a single dose of 20 or 40 mg parecoxib provided effective pain relief in 50 to 60% of patients when compared against placebo (15%).[5] Parecoxib is well tolerated and, at a higher dose, has a longer duration of analgesia with fewer patients requiring rescue medication over a 24 h period. Adverse events were generally mild to moderate in severity and were reported by just over half of treated individuals in both parecoxib and placebo groups.[5] Similarly, celecoxib is effective for acute postoperative pain as a single oral dose when compared with placebo and provides an alternative to more the commonly prescribed conventional NSAIDs.

Controversy surrounding COX-2 inhibitors

Cardiovascular safety

Although coxibs have a lower incidence of upper GI complications when compared with conventional NSAIDs, recent concerns about their cardiovascular safety have limited, and continue to limit, their use. They, like conventional NSAIDs, need to be regarded as double-edged swords with a potential for side-effects and serious complications.

The high-profile voluntary, worldwide withdrawal of rofecoxib from the market by Merck in 2004 was well documented. It was withdrawn as a result of a randomized, controlled trial detailed an increased risk of cardiovascular events associated with the drug.[4] Subsequent trials and meta-analyses confirmed this finding and debate has surrounded the cardiovascular safety of coxibs because coxibs, as a class, may cause an increased risk of thrombotic events (e.g. myocardial infarction and stroke) compared with placebo. This increased risk is dose-dependent and has been shown to be applicable to other coxibs as well as conventional NSAIDs with rofecoxib, etoricoxib, and diclofenac conferring an elevated thrombotic risk profile.[6] Naproxen and ibuprofen appear to have a lower cardiovascular risk profile.

In January 2010, The Medicines and Healthcare Products Regulatory Agency (MHRA) released their latest publication regarding this controversy concluding that increased thrombotic risk accounts for about three extra events per 1000 patient-years.[7] The increased risk relates mainly to myocardial infarction, and includes cerebrovascular and peripheral vascular events in some studies. For the majority of patients, the potential increase in the thrombotic risk is small. However, in patients with pre-existing risk factors for, or a history of, cardiovascular disease, the risk may be higher. Therefore, coxibs are contraindicated in patients with ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, and moderate or severe heart failure. Caution should be applied to patients with a history of left ventricular dysfunction, hypertension, oedema for any reason, and those with other risk factors for heart disease.[8]

Further market withdrawals of coxibs have occurred since 2004. In 2005, Pfizer voluntarily withdrew valdecoxib from the market in Europe and the USA predominantly because of concerns about serious skin reactions as well as ongoing concerns regarding cardiovascular safety. In 2007, Lumiracoxib became the latest coxib to be withdrawn after its marketing license was suspended in the European Union because of concerns over hepatotoxicity. Etoricoxib has been refused FDA approval in the USA but remains available in the UK with license for use in patients with osteoarthritis and rheumatoid arthritis.

Effect on platelet aggregation

NSAIDs, via non-selective COX-1 inhibition, reversibly inhibit thromboxane A2 production and, therefore, inhibit platelet aggregation and prolong bleeding time. Peri-operative conventional NSAIDs increase the risk of bleeding after a variety of operations compared with placebo and after tonsillectomy increase the risk of reoperation as a result of re-bleeding.[9] To date, coxibs have not been shown to have an adverse effect on peri-operative bleeding because of selective COX-2 inhibition and hence spare COX-1-mediated thromboxane A2 production.

Bone healing

The effect that conventional NSAIDs and coxibs have on bone healing has been identified as another cause for concern with reports suggesting they could inhibit the bone healing process. After a fracture, local release of prostaglandins occurs early as a result of the acute inflammatory response. COX-2 plays a critical role in this phase and its induction in osteoblasts is essential for bone healing. Animal studies have suggested that pharmacological inhibition or genetic manipulation to knock out the COX-2 gene leads to impaired bone fracture healing, but there is great diversity among data presented.[10] To date, no defining biological mechanism for the non-union or failure to unite has been proved. Evidence for an effect on bone healing in humans is also conflicting. Ketorolac has been linked to higher non-union rates after spinal fusion surgery, but studies are often of poor quality design with cofounders present. The data on coxibs are even scarcer with studies mainly limited to animal models and should not be extrapolated to humans, as variations in COX expression exist between species.[11] In the few human studies performed, coxib administration was short term with no adverse effects reported on bone healing. To conclude, there is no robust scientific evidence to discard the use of coxibs in patients suffering from a fracture especially if prescribing them for a short duration to treat acute pain. Equally lack of evidence does not constitute proof of the absence of an effect. It may be prudent to avoid coxibs in patients with other risk factors for impaired fracture healing such as smoking.

The future

Increased COX-2 expression appears to be involved in the development of cancer by promoting cell division, inhibiting apoptosis, altering cell adhesion, enhancing metastasis, and stimulating neovascularization.[12] Celecoxib derivatives have been manufactured which exhibit anti-carcinogenic activity and this has helped determine which chemical moieties of celecoxib have anti-carcinogenic properties. Future research into this area may focus on developing agents with high specificity for the COX-2 enzyme with fewer GI or cardiovascular side-effects.

Celecoxib and eterocoxib remain available in the UK under license for the relief of pain in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Parecoxib provides a short-term alternative to i.v. NSAIDs for acute postoperative pain. In chronic pain, safety concerns remain, and there are published recommendations for the use of coxibs (European League against Rheumatism, American College of Rheumatology, NICE and European Medicines Evaluation Agency).

Contrasting with the high profile given to the withdrawal of several coxibs, relatively little attention has been paid to acute pain management, and potential short comings, nationally and internationally. It is important to separate the issues surrounding long-term coxib use for chronic conditions from very short-term use for postoperative pain. The morphine sparing and multimodal roles of NSAIDs are well established in acute pain management. Single dose coxib administration, for example celecoxib and paracoxib, have been shown to be as effective as conventional NSAIDs and superior to placebo offering viable alternatives in the peri-operative period. The precise role of coxibs for short-term use is a question yet to be clarified, but in view of their cardiovascular safety profile they are contraindicated in patients with known atherosclerotic disease and those at risk of cardiovascular events. However, given the paucity of i.v. NSAID preparations with the exception of diclofenac, the case is strengthened for a parenteral coxib drug in short-term use in an acute peri-operative situation particularly in patients with a low risk of cardiovascular event. Devoid of bleeding risk, it can be administered pre- or intra-operatively and onset before awakening may reduce the need for additional pain relief in the early postoperative period. A similar case holds in areas of surgery such as head and neck surgery in which conventional NSAIDs may be avoided. Such adjunctive therapy could reduce patients' opioid requirements by 30–40%, with both improved pain relief and reduced opioid associated side-effects, such as nausea and vomiting.[11]

In summary, coxibs are useful as analgesic compounds with opioid sparing effects; however, caution must be exercised when prescribing them to minimize potential adverse events and contra-indications should be actively sought.

Declaration of interest

None declared.

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Please see multiple choice questions 17–20.