Review

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The Coxib NSAIDs: Potential Clinical and Pharmacologic Importance in Veterinary Medicine

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to control acute and chronic pain as well as to manage oncologic and neurologic diseases in human and veterinary patients. Despite ongoing research and efforts to improve the safety and efficacy of existing drugs, adverse effects such as gastrointestinal irritation, renal and hepatic toxicity, interference with hemostasis, and reproductive problems persist. The true incidence of NSAID-induced adverse effects in animals is unknown, but is likely underestimated, because cats and dogs may be more sensitive than humans to NSAIDs due to alterations in drug metabolism, absorption, and enterohepatic recirculation. NSAIDs produce both analgesia and toxic adverse effects primarily by inhibiting cyclooxygenase (COX), thereby decreasing the production of prostaglandins that signal inflammation and pain as well as mediate physiologic functions such as platelet aggregation, gastric protection, and electrolyte balance in the kidney. The presence of at least 2 COX isoforms may account for variability in NSAID efficacy and toxicity both within and among species. This paper reviews and evaluates the published literature on the safety, pharmacology, uses, and complications of a subclass of COX-1–sparing drugs, the coxibs, in veterinary medicine. Coxibs and other COX-1–sparing drugs provide a clinically useful improvement over traditional NSAIDs, but data are incomplete and more in vivo species-specific, target-tissue, and clinical studies are needed.

Key words: Arthritis; Cyclooxygenase; Nonsteroidal anti-inflammatory drugs; Toxicity.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used to control acute and chronic pain in both human and veterinary patients. Research on this group of drugs over the past decade has been intense, and although their principle therapeutic use is related to the musculoskeletal system, clinical use of coxibs has expanded into the fields of oncology and neurology. Despite widespread use, ongoing research to introduce new drugs of this class, and efforts to improve the safety and efficacy of existing drugs, adverse effects such as gastrointestinal (GI) irritation, renal and hepatic toxicity, interference with hemostasis, and reproductive problems persist. Every year, 100,000 humans are treated for adverse GI effects induced by NSAID use, and over 15% of these patients die from their complications.[1] The true incidence of NSAID-associated adverse effects in animals is unknown, but it is likely underestimated, as small animals such as cats and dogs may be more sensitive to NSAIDs as a consequence of differences in drug metabolism,[2,3] GI absorption,[4] and enterohepatic recirculation.[5] The number of adverse drug effects associated with NSAID use and reported to the Food and Drug Administration far exceeds any other companion animal drug, with hepatic, renal, GI, hematologic, nervous system, and urinary tract reactions reported most frequently.[6]

NSAIDs produce analgesia and toxic effects primarily by inhibiting a key enzyme in the arachadonic acid (AA) pathway, impairing the production of prostaglandins, most notably prostaglandin E_2 (PGE_2).[7] The AA pathway is initiated by damage to cell membranes, resulting in the release of prostanoids, which signal inflammation and pain, as well as perform physiologic functions on target tissues (Fig 1). NSAIDs block the rate-limiting step in this pathway at the site of cyclooxygenase (COX), an enzyme that converts arachadonic acid to prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2) through oxidation and reduction reactions.[7] The formed prostaglandins last only seconds to minutes before they are degraded to inactive compounds.[8] The presence and activity of two isoforms of the COX enzyme, a constitutive COX-1 and an inducible COX-2, have been investigated intensely since the early 1990s.[9] COX-1 is present under basal conditions in many cells, including platelets, mucosal cells in the GI tract, endothelial cells, and the renal medullary collecting ducts and interstitium.[10,11] In these tissues, COX-1 is associated with homeostatic physiological activities, such as platelet aggregation, gastric protection, and electrolyte balance in the kidney. The COX-2 isoform is present in low concentrations under basal conditions in monocytes, macrophages, smooth muscle cells, fibroblasts, and chondrocytes.[12] Recently, COX-2 mRNA, but not its protein, has been identified in the canine ovary, liver, lung, cerebral cortex, and GI tract.[13] The protein is rapidly inducible as a result of damaging stimuli from cytokines, growth factors, and bacterial toxins present at inflammatory sites, in infection, and in neoplasia.[14] Some proinflammatory cytokines, such as transforming growth factor-β, and steroids such as dexamethasone, have been shown to decrease COX-2 synthesis, whereas cytokines such as interleukin 1-β increase COX-2 mRNA transcription.[15–18] COX-2 has been shown to be constitutive in some tissues, such as kidney and brain, and plays a crucial role in the functions of these organs.[12,19–22] Many of the adverse effects of the nonselective NSAIDs (drugs that inhibit both COX-1 and COX-2 isoforms) have been attributed to inhibition of the constitutive COX-1. As a result, over the past decade, many COX-1–sparing drugs have been developed and introduced into clinical use for both the veterinary and human markets. This article reviews and evaluates the

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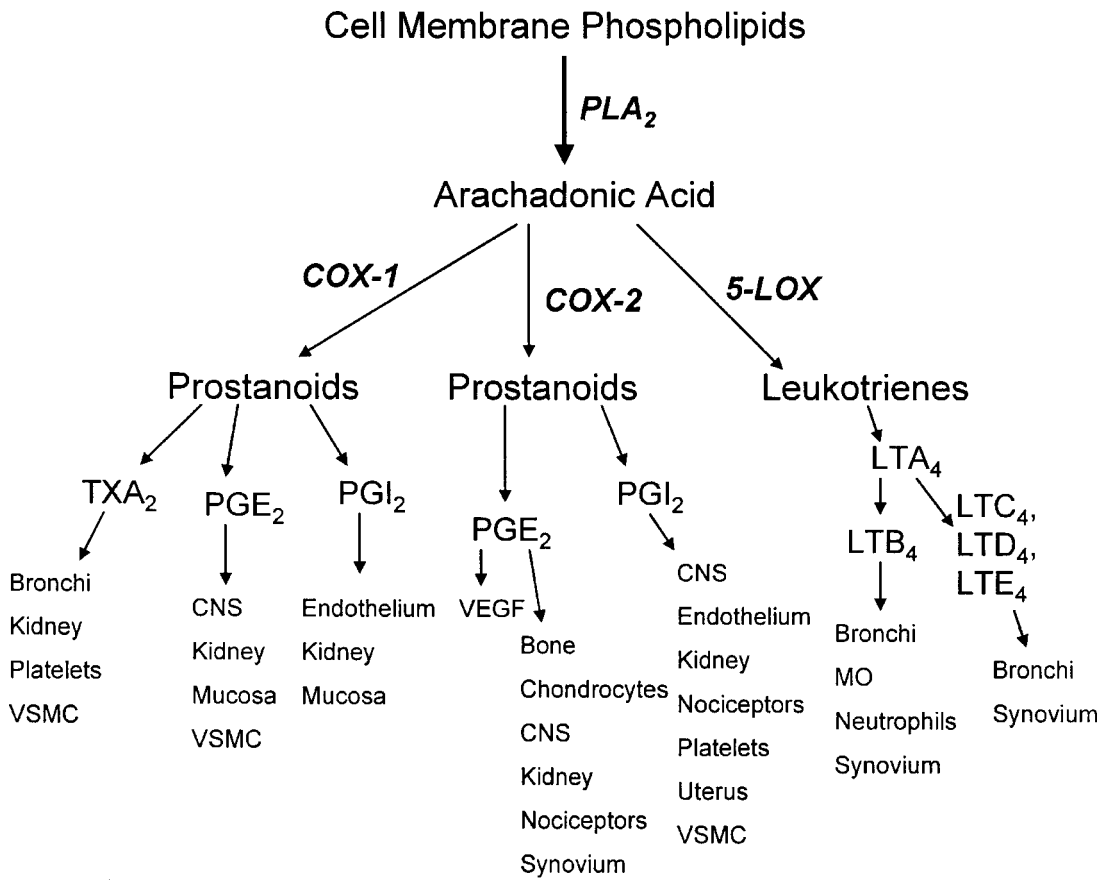

Fig 1. Metabolic pathway of arachadonic acid and examples of some target tissues of the prostanoids and leukotrienes. PLA_2 = phospholipase A_2; COX = cyclooxygenase; 5-LOX = 5-lipoxygenase; TXA_2 = thromboxane A_2; PGE_2 = prostaglandin E_2; PGI_2 = prostaglandin I_2; LT = leukotriene (A_4, B_4, C_4, D_4, E_4); VSMC = vascular smooth muscle cells; CNS = central nervous system; VEGF = vascular endothelial growth factor; and MO = macrophages.

published literature on the safety, pharmacology, uses, and complications of a subclass of COX-1–sparing drugs, the coxibs, in veterinary medicine.

Biochemistry

Although COX-1 and COX-2 have different physiologic functions, they are similar in structure. Both contain approximately 600 amino acids, have 60% amino acid homology,[23] and consist of a long hydrophobic channel with a hairpin turn at the end.[24] A single amino acid change in the hydrophobic channel allows selective drug inhibition.[25] For example, a valine residue at position 523, in place of an isoleucine, creates a larger pocket in the hydrophobic channel of COX-2, which allows larger molecules, such as the coxibs, to bind COX-2 but not COX-1.[26] Additional differences, such as the presence of a TATA box and binding sites for transcription factors (eg, nuclear factor-κB, nuclear factor for IL-6, cyclic AMP response binding element) in the promoter region of the immediate-early gene, are unique to COX-2.[27] The immediate-early gene present in COX-2 allows for its rapid expression secondary to appropriate stimuli; COX-2 mRNA and protein exist only transiently. In contrast, COX-1 does not have an immediate-early gene or a TATA box.[28]

Nomenclature

Although the term coxib is used rather loosely in the literature, often referring to any COX-1–sparing drug, true coxibs are a specific World Health Organization (WHO)–designated subclass of NSAIDs. The WHO states that their ''stem classification system [for drugs] is a working system to help to name new pharmaceutical active substances, rather than a classical pharmacological classification.''[a] With the exception of lumiracoxib,[b] all drugs with the suffix '-coxib' consist of a tricyclic ring and a sulfone or sulfonamide group[29]; lumiracoxib consists of 2 cyclic rings (Fig 2). These chemical features give the class of drugs its high specificity, saturability, and readily reversible binding behavior.[30] Coxibs, like all NSAIDs, inhibit COX-2, but their important feature is their sparing effect on COX-1. Through steric hindrance, their bulky structure limits inhibition of COX-1 when dosed appropriately to cause COX-2 inhibition. Frequently, the terminology ''COX-2 selective,'' ''COX-2 specific,'' or ''COX-2 preferential'' is used to describe specific NSAIDs, but these terms can be confusing, because they have not been quantified, are misleading, and frequently are misused.[31] For the purposes of this discussion, the term coxib refers strictly to the class of NSAID COX-1–sparing drugs with the suffix -coxib.

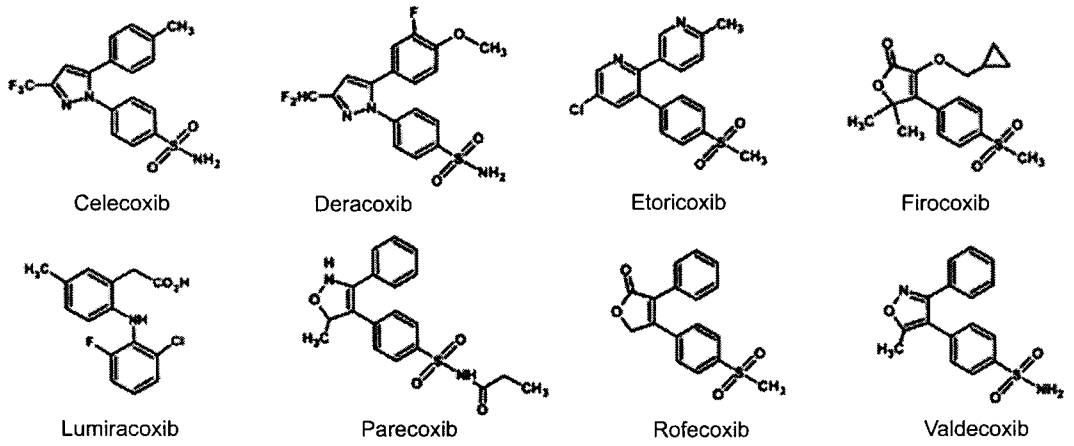

Fig 2. Biochemical structure of the coxib NSAIDs.

Worldwide, several coxib drugs have been introduced into human medicine, and others currently are under governmental review for use in humans. These compounds include 2 methylsulfones (rofecoxib[c] and etoricoxib[d]) and 2 sulfonamides (celecoxib[e] and the newer 2nd-generation compound, valdecoxib,[f] which also is available in an injectable form as the pro-drug parecoxib[g]). The newest coxib, lumiracoxib, is a phenylacetic acid derivative that has a shorter plasma half-life and a much higher affinity for COX-2 than other coxibs.[32,33] Several veterinary approved COX-1–sparing drugs are available, such as meloxicam,[h] etodolac,[i] and carprofen,[j] but only 2 coxibs (deracoxib[k] and firocoxib[l]) have been introduced to date.[13,34–36] The coxibs and other COX-1–sparing drugs have varying inhibitory potency for COX-2 versus COX-1, but it is unclear to what extent a higher degree of selectivity results in fewer adverse effects, because in vivo studies have revealed that drugs that are the least COX-1 sparing, such as celecoxib and meloxicam, do not inhibit COX-1 in human platelets when administered at normal dosages.[37] In dogs, carprofen, deracoxib, etodolac, and meloxicam have demonstrated COX-1–sparing properties in vivo, by sparing platelet production of thromboxane A_2 (TXA_2) and gastric mucosal production of PGE_1 and PGE_2, while simultaneously suppressing synthesis of whole-blood monocyte-derived PGE_2 and synovial fluid concentrations of PGE_2.[38,39] Several animal studies have revealed that COX-1–sparing NSAIDs are as efficacious as nonselective NSAIDs in providing analgesia,[40–42] while they significantly reduce the risk of GI ulceration associated with nonselective NSAIDs.[43,44]

Site of Analgesic Action

Although their sites of action still are unclear, coxibs and the other COX-1–sparing NSAIDs appear to produce analgesia at both central and peripheral concentrations. They inhibit the peripheral COX-2 enzyme to block the formation of prostaglandins such as PGE_2 and PGI_2, which function to dilate arterioles and sensitize peripheral nociceptor terminals to the actions of mediators such as histamine and bradykinin, which produce localized pain and hypersensitivity.[45] The PGE_2 produced by COX-2 plays a pivotal role in sustaining acute pain sensation by increasing the amount of cyclic AMP within nociceptors, thus decreasing their threshold of activation.[41] In addition to peripheral pain perception, COX-2-mediated prostaglandins such as PGE_2 are involved in spinal nociception[46] and central analgesia.[47] COX-2 is expressed in the brain and spinal cord and is upregulated in response to traumatic injury[48] and peripheral inflammation.[48–50] COX-2–activated PGE_2 lowers the threshold for neuronal depolarization, increasing the number of action potentials and repetitive spiking. The actions of COX-2 are thought to contribute to neuronal plasticity and central sensitization.[51,52] Coxibs are more lipophilic and less acidic than many nonselective NSAIDs such as aspirin and ibuprofen and can readily cross the blood-brain barrier, a property that may allow them greater systemic distribution and may facilitate efficacy on inhibition of the central regulation of COX-2.[53,54] One study found a significant increase in PGE_2 concentrations in cerebrospinal fluid after a noxious stimulus in the rat paw. PGE_2 concentrations returned to normal after administration of celecoxib but not after administration of a nonselective NSAID.[47]

Use in Arthritis

The mainstay of coxib use has been in the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). With these diseases, pro-inflammatory mediators such as interleukin-1 (IL-1), prostaglandins, and nitric oxide (NO) are produced by the synovial membrane and possibly the chondrocytes, which induce angiogenesis and inflammation of the synovium as well as drive the catabolism of cartilage and erosion of subchondral bone.[55] Cartilage destruction ultimately results from an imbalance between synthesis and breakdown of extracellular matrix molecules, notably proteoglycans, which in turn promotes an imbalance between cartilage destruction and effective cartilage repair.[56] COX-2 increases pro-inflammatory prostaglandins (eg, PGE_2) and IL-1β, which modulate cartilage proteoglycan degradation.[57] Prostaglandins may directly decrease chondrocyte proliferation[58] and inhibit aggrecan synthesis in chondrocytes as well.[59] COX-2 is upregulated in the synovium in patients with RA[60] and in chondrocytes obtained from both RA and OA patients.[61] Both PGE_2 and PGI_2 are present in synovial fluid from arthritic joints.[62] In laboratory studies,

however, the effects of COX-2 on cartilage differed depending on whether healthy or damaged cartilage was studied,[63,64] suggesting that other factors play a more important role in initiating the damage and that COX-2 potentiates such damage. Interestingly, COX-2 is constitutively expressed in rabbit chondrocytes, but not those of humans or cows.[63] In all 3 species, however, COX-2 is increased in response to IL-1, a known stimulant of cartilage destruction. Recent research supports the importance of NO as a co-factor in OA and RA, and future management of these diseases probably will involve COX-2 inhibitors as well as NO synthase modulators.[65–68]

Use in Oncology

Coxibs have revealed promising effects in controlling the growth of neoplastic cells and may have a therapeutic role in the prevention, treatment, and palliation of certain cancers. COX-2 is expressed on mesenchymal cells such as fibroblasts and macrophages and may potentiate tumor growth by stimulating the production of various growth factors (eg, VEGF, bFGF, HGF), angiogenesis, and tumor invasion.[69–72] Overexpression of COX-2 on epithelial cells has been shown to induce resistance to apoptosis[69] and to cause phenotypic changes resulting in increased adhesion to extracellular matrix proteins.[73] In studies of both human[74] and rat[75] colonic tissue, cancerous tissue had greater concentrations of PGE_2 compared to normal tissue. Increased expression of COX-2, but not COX-1, has been documented in colorectal carcinomas, and it is reported that approximately 85% of adenocarcinomas have a 2- to 50-fold increase in COX-2 expression at the mRNA and protein concentrations.[76,77] A study of naturally occurring colorectal tumors and polyps in dogs demonstrated that COX-2 was upregulated in pathologic tissue and absent in normal colonic and small intestinal tissue.[78] Similarly, in a study of transitional cell carcinoma of the bladder in dogs, COX-2 was not present in normal bladder tissue but was highly upregulated in all primary and metastatic tumors as well as in the surrounding blood vessels of several dogs.[79] Increased COX-2 expression also has been documented in lung,[80] gastric,[81] breast,[82] head and neck,[83] and pancreatic tumors,[84] and the use of coxibs to treat these cancers is promising.[85] Both celecoxib and rofecoxib reduce the incidence of adenomas and may even induce tumor regression.[86,87] Celecoxib also reduces the size of therapeutically resistant duodenal adenomas,[86] and it is the only coxib to be approved by the Food and Drug Administration for the treatment of familial adenomatous polyposis. In a rat model, celecoxib was shown to be superior to other NSAIDs in preventing and treating azoxymethane-induced carcinogenesis.[88] A recent retrospective study[89] identified a marked increase in median survival time when canine prostatic carcinomas were treated with carprofen or meloxicam, compared to a placebo. Nonselective NSAIDs, such as aspirin, also inhibit COX-2 and may have similar antineoplastic properties.[90]

Effects of Coxibs on Organ Systems

Gastrointestinal Tract

The primary site of NSAID toxicity is the GI tract in both human beings and companion animals.[4,91,92] Effects such as gastro-duodenal erosion, ulceration, perforation, and stricture have been associated with NSAID usage in several species.[5,93–95] These effects have been linked to inhibition of the cytoprotective effects of COX-1–induced synthesis of prostaglandins on the mucosal border, local irritation by the drug, and direct inhibition of platelet aggregation by decreased production of TXA_2.[42,96] When COX-1–sparing drugs are used, however, the incidence of these adverse effects was decreased (by approximately 50% in humans) but not eliminated, and the incidence was still significantly greater than with placebo in several controlled studies.[97,98] Interestingly, mice without the COX-1 gene do not spontaneously develop mucosal ulcerations or ulcers,[99] nor does the single use of the COX-1 inhibitor SC-560 or celecoxib in rats encourage this spontaneous development of ulcerations or ulcers. When both SC-560 and celecoxib were administered together, however, all rats developed mucosal erosions.[100] An independent study confirmed this finding with SC-560 and rofecoxib.[101] Thus, COX-2 appears to be protective for the mucosal border and important in maintaining mucosal health.[101] A very recent study[102] in dogs demonstrated decreased GI ulceration with licofelone,[m] a dual COX and 5-lipoxygenase inhibitor, when compared to rofecoxib, indicating that lipoxygenase may play an important role in mucosal metabolism in dogs. Although present at negligible concentrations in healthy tissue,[11] COX-2 expression is increased on the edges of gastric ulcers, where it indirectly accelerates ulcer healing by increasing angiogenesis by the inhibition of cellular kinase activity and upregulation of PGE_2 and VEGF in the gastric mucosa.[103,104] In a rat model, the use of the COX-1–sparing NSAID L-745,337 has been shown to delay gastric ulcer healing when compared to untreated controls,[105] supporting the importance of COX-2 in the ulcerative repair process. Immature animals may be more sensitive to the GI effects of coxibs, and animal safety studies for firocoxib on puppies identified adverse reactions at the above label dosage.[n]

Kidney

In the kidney, prostanoids regulate glomerular filtration rate (GFR), renin release, and sodium excretion. Inhibition of COX-1 previously had been assumed to be the cause of adverse effects such as salt retention, decreased GFR, hypertension, and edema associated with NSAID use, because COX-1 but not COX-2 is present in canine and rat renal arteries, arterioles, and veins.[106,107] Recent studies, however, have revealed that COX-2 is constitutively expressed in the macula densa, thick ascending loop of Henle, and interstitial cells in the dog[107,108] as well as in podocytes and the afferent arteriole in humans.[109] Activation of renin release by COX-2 in response to hypochloremia has been documented in animals,[110–112] and one study revealed that the activation of renin was due solely to COX-2, with no involvement of COX-1.[113] Additional studies have revealed that COX-2–derived PGE_2 is released from the macula densa, which causes vasodilatation in the afferent arteriole in the face of vasoconstriction produced by angiotensin II, norepinephrine, and vasopressin. Thus, blockade of this renal vasodilatory COX-2–induced PGE_2 may contribute to the decrease in GFR observed after NSAID use during

times of low effective circulating fluid volume. Volume depletion increased COX-2 expression in the canine and rat—but not in the monkey or human—macula densa and thick ascending loop of Henle.[107] Salt loading downregulates COX-2 expression in the renal cortex, but upregulates it in the inner medulla and vice versa, indicating that prostaglandins play varying roles in different regions of the kidney. Prostaglandins in the renal cortex protect glomerular circulation in times of decreased blood volume, and prostaglandins in the medulla promote diuresis and natruriesis in times of increased circulating blood volume.[114,115] A study in rats determined that the COX-1–sparing drug SC58236 significantly reduced medullary blood flow without modifying cortical blood flow, whereas a COX-1 inhibitor did not affect blood flow at any intrarenal site.[18] Thus, in diseases resulting in diminished or insufficient regulation of the renin-angiotensin-aldosterone system (eg, diabetes mellitus, hypoadrenocorticism), COX-2 is important for maintaining renal perfusion. Taken together, these findings support the possibility that coxibs and other COX-1–sparing NSAIDs might cause adverse effects on renal function in the presence of volume depletion, potentially leading to fluid retention, edema, hyperkalemia, and eventually acute renal failure. Animal safety studies of deracoxib identified a statistically significant ($P < .0009$) dose-dependent trend toward increased blood urea nitrogen (BUN) concentration in dogs receiving the drug over a 21-day period.[n] Additionally, rofecoxib has been shown to interfere with antihypertensive medications, specifically ACE-inhibitors and beta-blockers,[116] which rely on the vasodilatory prostaglandins for their actions.[117]

Bone

Recent studies have identified potential adverse effects of COX-2 inhibitors on bone metabolism. Rats and mice had delayed fracture healing when treated with celecoxib and rofecoxib compared with placebo.[118] The early phases of bone healing, when COX-2 mRNA concentrations, PGE, and PGF are highest,[119,120] are the most sensitive to the effects of coxib administration. COX-2 inhibition during this time may result in delayed healing or nonunion of the fracture site.[118] The effects of coxibs appear to be reversible, however, if the duration of administration is not prolonged.[121] COX-2 knockout mice achieve normal skeletal maturity, but do not have normal fracture healing. Consequently, it is believed that this isoform of the enzyme is important for signaling and orchestrating the complex processes of inflammation and intermembranous and endochondral ossification that occur only after fracture.[118] COX-2 regulates the genes *cbfa* and *osterix,* which are required for bone formation,[122] and COX-2–generated prostaglandins may alter bone metabolism by regulating osteoblasts. Prostaglandins have been shown to stimulate both bone formation and bone resorption, and their role in bone homeostasis is therefore complex and not fully understood.[123] Additionally, in a rat model, COX-2 accelerated the process of implant wear debris–mediated osteolysis in a rat model.[124] Moreover, COX-2 increased the concentration of inflammatory mediators such as tumor necrosis factor-β, IL-1β, IL-6, IL-11, IL-17, and other osteotrophic factors in response to the particulate wear debris.[125–128] As implant loosening continues to be an important complication in canine total hip replacement, coxibs may have some therapeutic role in attenuating this inflammatory response.

Cardiovascular System

The nonselective NSAID aspirin has been widely used for its cardio-protective actions, which result from inhibition of TXA_2 formation by platelets. TXA_2 causes platelet aggregation, vasoconstriction, and smooth muscle proliferation.[129] Aspirin has more affinity for COX-1,[130] but it affects both COX isoenzymes by irreversibly acetylating a serine residue and blocking binding of arachadonic acid to the enzyme's active site.[131,132] Inhibition of COX-2 causes a decrease in prostacylin (PGI_2) production by endothelial cells. PGI_2 causes vasodilatation, inhibits platelet aggregation, and has antiproliferative properties.[44] The actions of TXA_2 and PGI_2 thus are opposed, but it is believed that the inhibition of TXA_2 is responsible for both the therapeutic (ie, cardiovascular) and toxic (ie, gastrointestinal) effects of aspirin.[129] Aspirin's high affinity and irreversible binding cause altered function of the platelet. Platelets do not have nuclei and cannot synthesize new enzyme; thus, COX-1 is inhibited for the lifespan of the platelet. Coxibs, however, do not act irreversibly.[133] In a recent study,[134] atherogenesis was suppressed when both COX isoforms were blocked, but not when COX-2 alone was inhibited, indicating that prostanoids activated by COX-1 may be as, or more, important in atherogenesis. Theoretically, coxibs could increase the occurrence of a thrombotic event by blocking endothelium-derived PGI_2, resulting in an unopposed action of TXA_2, an endothelium-contracting and prothrombotic molecule.[135] This theory has not been supported in clinical trials of healthy adult humans.[136] However, results from the Vioxx Gastrointestinal Outcomes Research Study raised clinical concern by finding an increased rate of myocardial infarction with rofecoxib compared to naproxen,[44] and during the Adenomatous Polyp Prevention on VIOXX trial, Vioxx was pulled from the market due to an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke.[o] It is unclear whether or not cardiovascular risk is solely attributable to Vioxx, or if other coxibs may have similar effects. A second large-scale study, the Celecoxib Long-term Arthritis Safety Study, did not find an increased risk of myocardial infarction, but the study was not placebo-controlled, and patients were allowed to take daily aspirin concurrently.[137] Very recently, results of a randomized, controlled study, the Therapeutic Arthritis Research and Gastrointestinal Event Trial, were published.[138] This large study compared the efficacy and complications of lumiracoxib to naproxen and ibuprofen and found that lumiracoxib had similar efficacy with no increased risk of a serious cardiovascular adverse effects.

Reproductive System and Organ Development

The effects of COX-derived prostaglandins on the female reproductive tract and fetal development have been under investigation. Mice deficient in COX-2 are unable to ovulate[139] and have abnormal implantation and decidualization responses.[140,141] COX-2 is present in the uterine epithelium

in early pregnancy and may be involved in implantation, angiogenesis, and initiation of labor.[141,142] Additionally, COX-2 receptors have been found in the ductus arteriosus in rats. The secretion of prostanoids, especially PGE_2, may keep the ductus patent in utero, as indicated by the fact that treatment with coxibs prepartum causes premature closure of the vessel.[143,144] COX-2 is involved in development of the fetal and neonatal kidney in rats and mice. COX-2–deficient mice had significantly retarded development of the renal cortex, impaired glomerulogenesis,[145] and a higher neonatal death rate from renal failure.[139] Histological examination of the kidneys disclosed progressive nephron hypoplasia and tubular atrophy up to 6 weeks postpartum, supporting the hypothesis of a role for COX-2 in postpartum renal development.[99] Although data are limited and most drug labels do not specifically list pregnancy as a contraindication, prudence indicates that COX-2 inhibitors not be given to pregnant animals.

Nervous System

One of the relatively few documented roles for COX-2 as a constitutive enzyme is in the central nervous system (CNS). Basal concentrations of COX-2 are expressed within neuron cell bodies and dendrites at several sites in the brain, and this activity is especially high in neonates.[51,146,147] Release of prostanoids in the CNS serves to regulate body temperature, hyperalgesia, neuron development, and neuromodulation.[8,148,149] When induced by bacterial lipopolysaccharide (LPS) or IL-1β, COX-2 is upregulated in endothelial cells of blood vessels surrounding the hypothalamus and causes an increase in PGE_2, resulting in fever.[120,150,151] The possible role of COX-2 in neurodegenerative diseases, such as Alzheimer's disease (AD) in humans, has received growing attention, and studies currently are underway to elucidate disease mechanisms. Interest in the area began in the mid-1990s when epidemiological studies determined that the incidence of AD was lower in patients receiving a NSAID, especially if it was administered for 2 years before onset of disease.[152] No effect on the progression of AD was observed, however, if NSAIDs were given after the onset of neurological clinical signs.[153] COX-2 expression within neurons[154] is upregulated in the hippocampus and cortex in patients with AD and is directly associated with a decrease in neuronal function.[153] The molecular mechanisms are unclear, but COX-2–derived prostanoids accelerate neurodegeneration by potentiating glutamate excitotoxicity.[155] Interestingly, a recent clinical trial with celecoxib did not identify any change in AD,[156] whereas indomethacin[p] appeared to protect patients from the cognitive decline exhibited by a well-matched, placebo-treated group.[157] Additional studies are needed to elucidate the mechanisms responsible for neurodegeneration in humans and animals, but the data available indicate some role for COX inhibitors in the prevention or control of dementias.

Coxib Metabolism

Although some adverse effects of coxibs may be associated with concomitant NSAID use, preexisting organ insufficiency, or other systemic conditions, and differences in individual animal drug metabolism also may play a role in causing adverse effects. A study by Paulson et al[3] identified a polymorphism in cytochrome P450 in dogs that significantly altered the metabolism of celecoxib. They found that 55% of 99 dogs had slower clearance and longer elimination half-life of celecoxib as compared to accelerated metabolism of the drug in 45% of dogs. Less than 2% of dogs could not be classified into either group. Excessively short dosing intervals in dogs with prolonged drug metabolism of celecoxib could cause greater incidence and severity of adverse effects with this drug. Similar findings might apply to coxibs or other COX-1–sparing drugs, but published data are not available. Differences in biochemical characteristics among the coxibs also may account for variability in drug metabolism among individuals. Drugs that are highly lipophilic, such as celecoxib, are highly metabolized and as such have a large first-pass effect. On the other hand, rofecoxib is less lipophilic, experiences less extensive metabolism, a lower first-pass effect, and therefore therapeutic plasma concentrations may not be reached for an extended period of time in the dog.[158] Although some coxibs (eg, celecoxib, valdecoxib, deracoxib) have sulfonamide moieties, they do not appear to cross react with antimicrobial sulfonamides or produce the hypersensitivity reactions sometimes seen with sulfonamide drugs.[159,160] These properties are believed to be due to the lack of a primary arylamine, which leads to hydroxylamine and nitroso generation and secondary hypersensitivity.[161] To the authors' knowledge, no studies have been performed to specifically evaluate hypersensitivity reactions in dogs receiving a sulfonamide coxib.

Future Developments

COX-3

Although much research has been devoted to developing newer, safer, and more efficacious anti-inflammatory drugs, much still is unknown about the actions of NSAIDs, and in particular the role of COX isoforms. Although the expectations for COX-1–sparing drugs have been high, their introduction into human medicine has not eliminated adverse effects. A newly identified variant of the COX-1 isoform has recently been described.[162] It is similar to, yet distinct from, COX-1; its importance in the inflammatory pathway and disease pathogenesis appear to be different, and remains to be elucidated. This isoenzyme (COX-3) has been isolated from the cerebral cortex of dogs, and it is inhibited by acetaminophen, aspirin, diclofenac, and ibuprofen.[162] Its sensitivity to these drugs partially may explain the efficacy of these drugs in treating fever and controlling pain. Other variants of COX-1 and COX-2 recently have been identified, which may give more insight into COX metabolism.[162,163]

Lipoxygenase

Many studies have been undertaken to examine an alternative metabolic breakdown pathway of arachadonic acid, the leukotriene pathway (Fig 1). Inhibition of 5-lipoxygenase (5-LOX) inhibits synthesis of leukotrienes (LT). LTB4 is a potent chemotactic agent, and the peptidoleukotrienes cause smooth muscle contraction in airways and blood ves-

sels.[164,165] Dual COX-LOX inhibitors may have greater anti-inflammatory and analgesic properties, inhibit bronchoconstriction, and have few adverse effects on the upper GI tract.[166] A balanced inhibition of both pathways may provide superior anti-inflammatory effects, as well as reduce the adverse effects typically associated with NSAID use.[167,168] A COX-LOX inhibitor, tepoxalin,[q] recently has been licensed for use in dogs.

Nitric Oxide

The role of NO in inflammation continues to be studied. The NO synthase system is similar to the COX pathway, having both an inducible and constitutive pathway[169] as well as many roles in inflammation, cardiovascular physiology, and apoptosis.[170] NO may be involved as a fundamental mucosal defense agent in animal models,[171] and NSAIDs linked to NO retain their effectiveness without producing adverse GI effects.[172] However, despite promising preclinical studies and many years of research, clinical data in humans are limited, and no drug of this class has become available for veterinary use.[29]

Study Variability

Much interspecies variation has been noted among experimental models.[173,174] Within a species, notable differences between in vivo and in vitro models also are reported.[173,175,176] COX specificity has been different during in vitro studies compared to in vivo studies. The cause of this difference is not fully understood, but it has been hypothesized to be related to plasma protein binding and variable rates of dissociation of coxibs and other COX-1–sparing drugs from COX-2.[177] For example, some in vivo studies have reported COX-1–sparing activity of carprofen,[39] whereas some in vitro studies do not support that finding.[35] Additionally, knockout animal models may develop compensatory mechanisms, including different systemic responses to drugs.[99,178] Some non-COX molecular mechanisms not universally shared by all NSAIDs are inhibition of NF-κB, metalloproteinases, and inducible NO synthase as well as activation of PPARg.[178] These differences may explain some species variation and differences in therapeutic efficacy as well. Thus, care must be taken when extrapolating experimental evidence across species and among individual NSAIDs. Interspecies extrapolations from in vivo studies also should be made carefully.

In summary, coxibs and other COX-1–sparing drugs represent a clinically useful improvement over traditional NSAIDs. However, data are incomplete, and more in vivo species-specific, target-tissue, and clinical studies are needed. The future role of coxibs in veterinary analgesia, antipyresis, oncology, and geriatric patient care appear to be promising, but until more data are available, careful patient selection and monitoring are indicated.

Footnotes

[a] Personal communication with Dr Raffaella G. Balocco Mattavelli, Responsible Officer, WHO International Nonproprietary Names (INN) Programme, e-mail correspondence on September 16, 2004

[b] Prexige®, Novartis, Basel, Switzerland

[c] Vioxx®, Merck & Co, Whitehouse Station, NJ

[d] Arcoxia®, Merck & Co, Whitehouse Station, NJ

[e] Celebrex®, Pfizer, New York, NY

[f] Bextra®, Pfizer, New York, NY

[g] Dynastat®, Pfizer, New York, NY

[h] Metacam®, Boehringer Ingelheim Vetmedica Inc, St. Joseph, MO

[i] EtoGesic®, Fort Dodge Animal Health, Overland Park, KS

[j] Rimadyl®, Pfizer, New York, NY

[k] Deramaxx™, Novartis Animal Health US, Greensboro, NC

[l] Previcox®, Merial, Duluth, GA

[m] ML-3000, Merckle GmbH, Ulm, Germany

[n] Freedom of Information Summary, NADA 141230, PREVICOX Chewable Tablets (firocoxib), July 21, 2004

[n] Freedom of Information Summary, NADA 141-203, DERAMAXX Chewable Tablets (deracoxib), August 21, 2002

[o] Merck announces voluntary world-wide withdrawal of Vioxx®, Merck & Co, Whitehouse Station, NJ. Press release September 30, 2004

[p] Indocin®, Merck & Co, Whitehouse Station, NJ

[q] Zubrin™, Schering-Plough Animal Health, Kenilworth, NJ

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