Non-Steroidal Anti-inflammatory Drugs (NSAIDs) in Reptiles and Amphibians: A Review

David Hannon, DVM, DABVP (Avian)

Session #020

Affiliation: From Avian and Exotic Animal Veterinary Services, Memphis Veterinary Specialists, 555 Trinity Creek Cove, Cordova, TN 38018, USA.

Abstract: Non-steroidal anti-inflammatory drugs are commonly used in veterinary medicine for managing acute and chronic pain and inflammation. Although they are used extensively in reptiles and amphibians, there are very few pharmacokinetic or pharmacodynamic studies of the use of these drugs in these species in the literature. This master class will review these drugs and their methods of action, and look at the safety, efficacy, toxicity, and recommended usage in reptiles and amphibians.

Cyclooxygenase and Prostaglandins

In 1971 it was discovered that aspirin inhibited the activity of a cyclooxygenase enzyme 1 (COX-1) that produced prostaglandins (PGs) involved in the pathogenesis of fever, pain, swelling, and inflammation. In the following 30 years, 2 more enzymes also would be discovered, COX-2 and COX-3. Cyclooxygenase oxidizes arachidonic acid to various eicosanoids, including prostaglandins. The initial prostanoid formed is prostaglandin hydroperoxide (PGH₂), which is then converted to PGH₁. PGH₁ is then converted by prostaglandin E-synthetase to PGE₂, by prostaglandin D-isomerase to PGD₂, by prostaglandin F-reductase to PGF₂, by prostacyclin synthetase to PGI₂ (prostacyclin), and by thromboxane synthetase to thromboxane A₂ and B₂ (TXA₂, TXB₂). Arachidonic acid is also oxidized by 5-lipoxygenase (5-LOX) to form leukotrienes. Prostaglandins have a short half-life (4-6 min at 37°C), so they are subsequently synthesized constantly and not stored by the body. They tend to act locally at the site of production.

The COX enzymes each have different roles. COX-1 produces prostaglandins that are involved in mucosal defense, such as secretion of mucus and bicarbonate, attenuation of constriction of mucosal blood vessels, and regeneration of mucosal epithelium. It generates TXA₂, which is necessary for normal platelet function. It also has a cytoprotective function in some tissues, including the gastric mucosa, kidneys, reproductive tract, and central nervous system. COX-2 generates prostaglandins that exert anti-inflammatory effects by the inhibition of leukocyte adherence, prevent mucosal erosions and promote healing of these lesions, and play a role in the protection and maturation of the kidneys. COX-3 produces prostaglandins that initiate fever. Depending on the NSAID that is selected, expected effects can not only include decreased inflammation, but also alteration of platelet function, modulation of vascular tone in the gastric mucosa and kidneys, cytoprotective functions within the gastric mucosa, smooth muscle contraction, and alteration of body temperature.

Prostaglandins are important local mediators of pain and inflammation. Of the prostaglandins, PGE₂ and prostacyclin are the most potent mediators of pain and inflammation. They exert a hyperalgesic effect, and they enhance noiception produced by other factors, such as bradykinin. The COX-2 isoenzyme is upregulated in inflammatory states (up to 20 times its basal levels) and plays a key role in nociception, whereas COX-1 is produced constitutively and also plays an integral role in nociception. Prostaglandins are also known to lower activation thresholds to mechanical, thermal, and chemical stimulation. It has also been shown that NSAIDs produce much of their analgesic effects by inhibiting COX activity centrally.
Different NSAIDs have been noted to have different effects on COX enzymes. Most NSAIDs that inhibit COX will divert arachidonic acid to the 5-LOX pathway, subsequently increasing the synthesis of leukotrienes, which have been implicated in the creation of NSAID-induced gastric ulcers. Some newer NSAIDs will also inhibit 5-LOX.50

**COX and Prostaglandins in Reptiles and Amphibians**

**Inflammation**

Royal et al evaluated traumatized versus normal tissues for COX protein expression in eastern box turtles. They found that traumatized muscle tissue had statistically significantly increased COX-1 and statistically insignificant increased COX-2 compared to normal muscle. The highest levels of both COX-1 and COX-2 were noted in the liver and kidney, but these levels were not significantly different in traumatized or non-traumatized turtles. They suggest that NSAIDs that block both COX-1 and COX-2 might be more efficacious in eastern box turtles than COX-2 selective drugs, and that these drugs need to be evaluated further for potential liver and kidney toxicity.105 Sadler et al looked at COX expression in normal and traumatized skin and muscle in ball pythons. They found that COX-1 expression was significantly increased in inflamed skin tissues compared to normal skin, but that there were not any significant changes in the expression of either COX-1 or COX-2 in inflamed muscle tissues compared to normal muscle.107 They also suggest that a non-specific NSAID may be more effective in reptiles than a COX-2 selective drug.

**Cardiovascular system**

Robleto and Herman evaluated the cardiovascular effects of PGI2 and PGF2α in unanesthetized bullfrogs. They found that both PGs increased the heart rate (independent of the autonomic nervous system), but had differing effects on the mean arterial pressure; PGI2 was hypotensive while PGF2α was hypertensive.102

**Urinary system**

In mammals, it has been shown that prostaglandins normally cause vasodilation of the afferent arterioles of the glomeruli, thereby maintaining a normal glomerular perfusion and glomerular filtration rate (GFR).50 However, this has not been studied in reptiles and amphibians. PGE1 and PGE2 are known to interfere with the water permeability effect of vasopressin in the toad urinary bladder and kidney.87 Forrest and Goodman showed that PGE3 inhibits the action of vasopressin in the toad urinary bladder.35 In 1977, Zusman et al discovered that vasopressin stimulated PGE biosynthesis in the urinary bladder of Bufo toads, and that the water permeability response of the bladder to vasopressin was subsequently inhibited by PGE.144 In 1978, Orloff and Zusman found that in the toad urinary bladder and kidney, vasopressin increases the release of arachidonic acid, and subsequently PGE2.87 Herman et al (1981) looked at the effects of prostaglandins and prostaglandin precursors on osmotic water flow in the anuran urinary bladder. They found that PGE1, PGE2, and PGI2 inhibited water flow, as did arachidonic acid, which was converted to PGD2 and PGE2. Eicosapentaenoic acid was converted to PGD3 and PGE3, which had an opposite effect.60 In 1982, Arruda showed that in turtle and toad bladders, high intracellular calcium inhibits water transport via prostaglandin release, but the inhibition of sodium or H+ transport was independent of prostaglandins.8 Also in 1982, Forrest et al found that PGE3 is and no other PGs are responsible for acidification in the toad urinary bladder.36 In 1985, Schondorf and Šatriano noted that in the toad urinary bladder, vasopressin stimulated PG synthesis in a cAMP-independent manner, and inhibited PG synthesis in a cAMP-dependent manner.111 Sabatini (1986) found that the effect of PTH on water flow in the toad urinary bladder is mediated by an increased cellular uptake of Ca that stimulates PG release, and that PG
release, in turn, appears to mediate the inhibitory effect of PTH on vasopressin-stimulated water transport. In 1991, Yorio et al demonstrated that in the toad urinary bladder, PGE\textsubscript{2} inhibited H\textsuperscript{+} excretion at lower doses, but enhanced it at higher doses. He also found that toads that were maintained under chronic metabolic acidosis had enhanced H\textsuperscript{+} excretion rates and a threefold increase in cellular PGE\textsubscript{2} concentrations.

**Reproductive system**

Prostaglandins have extensive involvement in the reproductive system. They are associated with ovulation, oviposition, and luteal function. In reptiles, prostaglandins have been shown to stimulate oviducal contractions, which may be overridden by neural control, which can subsequently result in egg retention. Jones et al demonstrated that a prostaglandin inhibitor (indomethacin) delayed FSH-induced ovulations, lowered PGE secretion, and inhibited preovulatory changes in the follicular wall in anoles. Mahmoud et al showed that a single injection of PGF\textsubscript{2\alpha} in recently ovulated snapping turtles induced early luteolysis and a significant decrease in plasma progesterone levels. Late pregnancy in common geckos, a viviparous species, could not be induced to give birth with high doses of PGF\textsubscript{2\alpha} unless the animal was pretreated with a β-adrenergic antagonist in vivo, whereas in vitro, administration of PGF\textsubscript{2\alpha} caused uterine contraction, which could be blocked by administration of a β-adrenergic agonist. In 1992, Gobbetti et al showed that in the brains of crested newts, PGF\textsubscript{2\alpha} is involved in the post-reproduction processes through estradiol secretion, while PGE\textsubscript{2} was involved in the reproductive processes, possibly through androgen secretion. In 1994, Gobbetti et al studied prostaglandins in the brains of Italian wall lizards during reproduction and found that PGF\textsubscript{2\alpha} levels were elevated during the refractory phase of the reproductive cycle, whereas PGE\textsubscript{2} levels were decreased. They also determined that levels of PGF\textsubscript{2\alpha} were increased after treatment with salmon GnRH, and decreased by substance P and acetylsalicylic acid. Dubois and Guillette demonstrated that the uteri of alligators secrete PGE and PGF\textsubscript{2\alpha} at varying levels depending on the reproductive status of the animal. In 1994, Gobbetti et al looked at prostaglandins in the reproductive cycle of male Italian wall lizards, and found that testicular androgen synthesis during the fighting phase is under the control of PGE\textsubscript{2}, whereas 17\beta-estradiol synthesis during the refractory phase is regulated by PGF\textsubscript{2\alpha} in the testes, and by PGE\textsubscript{2} and PGF\textsubscript{2\alpha} in interrenal cells. In 2006, Jones et al looked at the interactions between uterine tension, PGs, calcium and AVT in the uteri of anoles, and noted that indomethacin blocked the AVT-induced tonic contractions in stretched uteri, and that the interval between contractions was decreased by PGF\textsubscript{2\alpha} and PGE\textsubscript{2}, an effect that was also blocked by indomethacin.

In amphibians, Guillette et al noted that ovarian and oviducal PGF\textsubscript{2\alpha} acts like an endocrine hormone, coordinat- ing oviducal contractions and CNS-controlled oviposition behavior. Diakow and Nemiroff showed that PGE\textsubscript{2} and PGF\textsubscript{2\alpha} affect female mating behavior in leopard frogs, and that vasotocin acts in part through a mechanism that involves prostaglandin synthesis. In 1992, Gobbetti and Zerani showed that testicular PGF\textsubscript{2\alpha} was lower in the post-reproduction phase in edible frogs, and that administration of mammalian GnRH increased its levels during the pre-reproduction and reproduction phases. In crested newts, testicular PGF\textsubscript{2\alpha} levels were lower during the reproduction phase, and administration of GnRH increased its levels during the pre-reproduction and reproduction phases. They also showed that PGF\textsubscript{2\alpha} levels were increased in ovulating edible frogs, and it may be involved in the control of egg deposition in this species. In 1993, Gobbetti and Zerani showed that in edible frogs, a seasonal increase in plasma PGE\textsubscript{2} may inhibit breeding activity by stimulating ovarian androgen secretion, whereas a seasonal increase in plasma PGF\textsubscript{2\alpha} may inhibit breeding by stimulating ovarian estradiol secretion. In 1995, Chang et al demonstrated that elevated levels of PGF\textsubscript{2\alpha} are associated with spontaneous hormone-induced ovulation, and that protein kinase C mediates gonadotropin induction of PGF\textsubscript{2\alpha} in the ovaries of *Rana sp.* In leopard frogs, Schuetz noted that normal synchronization and maturation of oocytes may require the combined action of steroids and prostaglandins acting within different follicular compartments. Ramos et al found that PGF\textsubscript{2\alpha} increased ovulation induced by a pituitary homogenate in toad ovaries, whereas PGE\textsubscript{1} had an inhibitory effect on ovulation.
**Gastrointestinal system**

The roll of prostaglandins in the protection of the gastrointestinal (GI) mucosa is well known. In 1979, Garner et al showed that PGE2, 16,16-dimethyl PGE2, and PGI2 all inhibited H+ secretion from the gastric mucosa of the European frog, whereas only 16,16-dimethyl PGE2 stimulated bicarbonate secretion, and it also prevented the inhibitory action of indomethacin on bicarbonate secretion.41 Also in 1979, Garner and Heylings demonstrated that 16,16-dimethyl PGE2 inhibited H+ secretion and stimulated bicarbonate secretion in the fundus of the common frog, and that PGF2α increased bicarbonate secretion in the fundus of salamanders, but had no significant effect on H+ secretion.40 Alkali transport by the proximal duodenum of the bullfrog showed a dose-dependent increase upon administration of PGE2, 16,16-dimethyl PGE2, and PGF2α with an increased response to the E-type PGs than to PGF2α.34 In 1982, Takeuchi et al found that in isolated American bullfrog gastric fundic mucosa, PGs at low concentrations had an inhibitory effect on histamine-stimulated H+ secretion, but at higher concentrations, they stimulated H+ secretion by releasing histamine from mast cells.128 In 1995, the same group reported that ulceration of isolated bullfrog gastric mucosa in the presence of acid depends upon either a deficiency of endogenous PGs or a lack of nutrient bicarbonate.129

**Integument**

Page and Yorio showed that PGF2α exhibited a dose-dependent inhibition of acidification of the abdominal skin of the southern leopard frog, by maintaining a low basal H+ excretion rate and regulating intracellular pH. Administration of PGE2 and PGF1α showed no significant alteration in H+ excretion rates.90 In 1991, Yorio et al showed that the abdominal skin of southern leopard frogs pretreated with ibuprofen had enhanced H+ excretion similar to frogs with chronic metabolic acidosis, and that this effect was inhibited by administration of PGF2α.142

**Fever**

The concept of behavioral fever has been well-documented in reptiles16,58 and amphibians.138 In 1981, Hutchison and Erskine discovered that injections of PGE1 (a known pyrogen) into the third ventricle of the brain of common mudpuppies produced a long-lasting behavioral fever, with animals selecting locations with temperatures averaging nearly 5°C greater than baseline for up to 48 hours post-injection.65 In 2002, Bicego et al showed that Rococo toads injected with indomethacin did not seek a warmer temperature compared to controls when injected with pyrogenic lipopolysaccharides.13 Seebacher and Franklin found in 2003 that bearded dragons had a higher heart rate during warming than during cooling, and this effect was negated with administration of COX-1 and COX-2 inhibitors, and enhanced by prostacyclin and PGF2α but not by thromboxane B2.114 However, in 2006 they noted that this same effect did not occur in saltwater crocodiles.115 In 2005, Chingbin et al noted that this effect only occurred in Przewalski’s toadhead agamas below 25°C.70 It has been hypothesized that central processing of peripheral thermal information may involve COX enzymes that have a bearing on cardiovascular response, and that this response to heating and cooling in reptiles is at least in part mediated by the integration between the baroreflex and systemically-acting nitric oxide synthase and COX enzymes.116

**Other prostaglandin effects**

In 1981, Delarue et al found that exogenous prostaglandins can control corticosteroid production in marsh frogs, that endogenous prostaglandins are required for spontaneous biosynthesis of corticosteroids, and that endogenous prostaglandins are not involved in ACTH-induced steroidogenesis.23 In 1983, Perroteau et al showed evidence that a physiological relationship between the kidney and interrenal gland may exist in frogs, and that the action of angiotensin II on both corticosterone and aldosterone production may be mediated by prostaglandins.93
In 1987, Ferrary et al found that the inner ear of the frog produces PGI$_2$ and PGE$_2$, and that prostaglandins could be involved in the physiology of the inner ear.$^{32}$

In 1990, Ajayi and Okpako studied effluents from the lungs of rainbow lizards, and found high contents of a PGE$_2$-like prostanoid, the release of which was blocked by COX inhibitors.$^{39}$

In 1997, Herman et al found that whole blood, purified erythrocytes, and leukocytes activated by clotting obtained from western rat snakes produced thromboxane, PGE$_2$, and 5-LOX, and that inhibition of clotting in this species was achieved with administration of indomethacin.$^{62}$

Sharma and Suresh showed in 2008 that when the production of PGE$_2$ was blocked by COX inhibitors, tail regeneration after autotomy was significantly delayed in northern house geckos.$^{117}$ In 2015, Narayanan found that COX inhibitors not only blocked PGE$_2$, but also blocked fibroblast growth factor-2 (FGF$_2$), another contributing factor in the tail regrowth of house geckos.$^{85}$

In 1985, Schmidt showed that administration of progesterone and arginine vasotocin concurrently with PGF$_{2\alpha}$ increased mating call phonotaxis in female American toads, whereas administration of PGF$_{2\alpha}$ alone had minimal effect.$^{112}$ In 2009, Gordon and Gerhardt repeated this work by assessing phonotaxis in female gray treefrogs, and found that concurrent administration of PGF$_{2\alpha}$- and progesterone-treated animals exhibited phonotaxis more often than untreated controls.$^{49}$

### Pain Perception in Reptiles and Amphibians

Although peripheral nociceptors have not been directly observed in most reptiles, they have been documented in amphibians, as well as mammals, birds, and fish.$^{120}$ Thermosensitive and thermomechanosensitive nociceptors have been identified in the trigeminal ganglia of pit vipers, and mechanonociceptors have been identified in the cutaneous plantar nerve in American alligators.$^{120}$ Substance P is a peptide that is present in peripheral nerves and the spinal cord, and is expressed with painful stimuli in mammals. It is highly conserved across vertebrate species, and has been documented in the nervous system of several species of turtles.$^{120}$

Nociceptive pathways have not been extensively studied in reptiles and amphibians, but in mammals prostaglandins exert hyperalgesic effects and enhance nociception produced by other mediators, such as bradykinin.$^{50}$ The anti-nociceptive effects of NSAIDs are exerted both centrally and peripherally. Peripherally, NSAIDs penetrated inflamed tissues and have a local effect, while the central effect is at both the spinal and supraspinal levels, with contributions from both COX-1 and COX-2.$^{50}$ Reptiles and amphibians have pathways similar to the mammalian pathways that perceive pain and nociception, so the presumption that these pathways work in the same manner is sound, but there has been very little research done to confirm this.$^{120,126}$

Behavioral and physiological parameters typically associated with pain in reptiles include the absence of normal behavior, a hunched posture, increased aggression, rubbing or scratching a specific area of the body, skin color changes (particularly darkening), lameness, decreased food consumption, decreased activity, changes in response to stimulation (increased or decreased), stinting on palpation, keeping eyes closed, ataxia or lameness, and changes in heart or respiratory rates.$^{14,120}$ Chelonians may keep their heads extended away from the body and ventrally directed.$^{14,120}$ Snakes may hold their bodies less coiled at the site of pain.$^{14}$ Amphibians may show increased aggression, immobility or lethargy, closed eyes, lameness or ataxia, an increased flight response, anorexia, color changes, rapid respiration, and they may flick their foot or bite at the affected area(s).$^{14}$
Individual NSAIDs in Reptiles and Amphibians

**Aspirin (acetylsalicylic acid)**

Willow bark contains salicylic acid, and its anti-inflammatory effects have been documented as far back as Hippocrates (460-377 BC). Salicylic acid was first isolated in 1763, and acetylsalicylic acid (ASA) was first created in 1853. In 1900, Bayer marketed the first commercial aspirin product.\(^5^0,^5^7\) Aspirin inhibits COX-1, inhibiting the production of PGs and TXA\(_2\), resulting in analgesic, antipyretic, and anticoagulative effects. Even though it does not directly inhibit COX-2, it can modify it to produce, in conjunction with 5-LOX, aspirin-triggered lipoxin (ATL), which appears to have a protective effect on the gastric mucosa. In mammals, aspirin can cause an irreversible reduction in platelet aggregation. It is primarily metabolized in the liver and excreted through the kidneys.\(^9^4\)

Aspirin has been documented to have varying effects in reptiles and amphibians. In 1976, Bernheim and Kluger showed sodium salicylate injections in desert iguanas resulted in a dose-dependent attenuation of a febrile response.\(^1^1\) Gobbetti et al noted that ASA decreased PGF\(_{2\alpha}\), estradiol, and aromatase activity, and increased androgen production in the brain of male Italian wall lizards.\(^4^8\) In 1999, Stewart and Hudspeth found that prolonged administration of ASA produced a marked but reversible suppression of spontaneous otoacoustic emissions in the ears of Tokay geckos.\(^1^2^7\) In 2005, Ahmed et al showed that ASA induces hyperprolactinemia in Indian spiny-tailed lizards.\(^2\)

In amphibians, it has been noted that aspirin potentiates the hydromosotic effect of antidiuretic hormone (ADH) in the toad urinary bladder.\(^9^1\) In 1898, aspirin was shown to have a negative inotropic effect on frog hearts.\(^5^7\) In 1976, Hall et al showed that it decreased sodium transport across isolated common frog skin in vitro.\(^5^6\) In 1977, Spenney and Bhown looked at the effects of ASA on the bullfrog gastric mucosa, and found that it caused changes in transmucosal resistance, mucosal permeability, and a reduction in mucosal ATP and phosphocreatine.\(^1^2^2,^1^2^3\) In 1986, Rowe et al showed that ASA causes inhibition of \(\text{H}^+\) secretion in isolated gastric mucosa from American bullfrogs.\(^1^0^4\) In 1989, Ashley et al found that under acidic conditions, aspirin increased the permeability of the gastric mucosa in mudpuppies.\(^7\) ASA caused mucosal ulceration in isolated bullfrog stomachs, even when bathed in a bicarbonate-rich solution.\(^1^2^9\) Aspirin reduced PGE\(_2\) and PGI\(_2\) production by ampulla and duct tissue isolated from the frog posterior semicircular canal.\(^3^2\) In 1989, Puel et al found that ASA suppressed spontaneous activity, water motion evoked excitement, and the increase in afferent nerve activity in hair calls evoked by L-glutamate and kainic acid in a dose responsive manner in the lateral line of African clawed frogs. This response was similar to its effects on mammalian hair cells in the cochlea.\(^9^5\) In the isolated lenses of leopard frogs, aspirin (which is believed to influence cataract development) was shown to slow the recovery of depolarization of membrane potential, the decrease in membrane resistance, and the increase in internal resistance caused by acidification.\(^7\) In 1994, Nandi et al found that aspirin enhanced histamine-stimulated \(\text{H}^+\) release in the gastric mucosa of frogs.\(^8^4\) The critical effect environmental contamination concentrations of acetylsalicylic acid on aquatic animals, including amphibians, has been calculated.\(^3^3\)

**Acetaminophen**

Acetaminophen was first marketed as Paracetamol in 1887. Its mechanism of action is not completely understood, but it produces analgesia and antipyresis by weak inhibition of COX-3. It does not have any significant anti-inflammatory effects, nor does it inhibit platelet function.\(^9^4\) In animals, its toxic effects (methemoglobinemia, liver necrosis, keratoconjunctiva sicca (KCS), etc.) have been well-documented.\(^9^4\)
In 1970, Urakabe et al documented that acetaminophen enhanced water permeability when applied on the serosal surface of Japanese common toad bladders in vitro.\(^{118,133,134}\) Also in 1970, Shirai noted that acetaminophen had a theophylline- and vasopressin-like effect on the toad bladder.\(^{119}\) In 1976, Hall et al found that acetaminophen decreased sodium transport across the skin of common frogs in vitro.\(^5\) In 1991, Bhatt et al demonstrated that the addition of penetration enhancers increased transportation of acetaminophen through shed snake skin.\(^1\)

Acetaminophen is considered a common wastewater contaminant, and its effects on amphibian larvae have been well documented. Fraker and Smith showed that it caused a decrease in the activity levels of leopard frog tadpoles when they were exposed to it concurrently with caffeine, and on African clawed frog tadpoles when combined with triclosan.\(^{37,38}\) Smith and Burgett showed that had a negative effect on the activity level of American toad tadpoles, and at higher doses decreased survival.\(^{121}\) In 2006, Richards and Cole showed that the maximum concentration of ibuprofen detected in surface waters had no significant toxicity, teratogenicity, or growth inhibition in \textit{Xenopus} tadpoles.\(^{100}\) The critical effect environmental contamination concentrations of acetaminophen on aquatic animals, including amphibians, has been calculated.\(^{33}\)

Acetaminophen has been used to poison brown tree snakes in Guam. An 80 mg dose of acetaminophen administered to brown tree snakes resulted in 100% mortality.\(^{108}\) It has subsequently been distributed in dead rodent baits, which have been successful in reducing snake populations while having a minimal effect on non-target feral and wildlife species.\(^{66,108}\) It is being investigated for similar use to control invasive Nile monitors, Burmese pythons, and black spiny-tailed iguanas in Florida.\(^8,76\)

**Dipyrone (Metamizole)**

Dipyrone was discovered in 1921. Its exact mechanism of action is unknown, but it is thought to behave similar to acetaminophen in that it has analgesic and antipyretic effects thought to be the result of blocking the formation of PGD and PGE, which are endogenous pyrogens, but it has a minimal anti-inflammatory effect.\(^{98}\) It has been studied in amphibians, and has been found to cause a regression in curarimimetic effects in the skeletal muscle of frogs.\(^{98}\)

**Phenylbutazone**

Phenylbutazone was discovered in 1949. It inhibits both COX-1 and COX-2, although its effects on COX-1 are significantly greater. It has primarily been used in horses and dogs for its anti-inflammatory, analgesic, antipyretic, and mild uricosuric properties.\(^{94}\) In 1970, it was found to enhance the permeability of the toad urinary bladder when applied to the serosal surface in vitro.\(^{118,119,133,134}\) Also in 1970, Breull and Karzel found that phenylbutazone had a calcium-like effect on the membrane resting potential of frog skeletal muscle fibers in vitro.\(^15\) It was reported to cause a decrease in sodium transport across common frog skin in vitro.\(^5\) In 1985, Madden and Van der Kloot found that phenylbutazone altered transmissions at the neuromuscular junctions of frogs.\(^72\)

**Ibuprofen**

Ibuprofen was discovered in 1961. It is a non-selective COX inhibitor, with its anti-inflammatory, analgesic, and antipyretic effects thought to be due to inhibition of COX-2, while side effects, such as GI ulceration, are thought to be caused by its inhibition of COX-1.\(^5\) In 1977, Zusman et al found that, in the urinary bladders of \textit{Bufo} toads, ibuprofen had no effect on basal water flow or on cAMP-stimulated water flow, but it did block PGE synthesis and increased vasopressin-stimulated water flow.\(^{144}\) In 1981, Rees et al found that ibuprofen inhibited fundic alkaline secretion in the stomachs of salamanders and bullfrogs, and that the effect was reduced with the addition of PGE\(_2\).\(^99\) In 1982, Arruda showed that ibuprofen significantly decreased the inhibitory effect of high
extracellular calcium on vasopressin-stimulated water flow in the toad urinary bladder, and that it blunts the effect of agents which increase intracellular calcium on water transport, but had no effect on sodium or H⁺ transport.\(^6\)

Schlondorff and Satriano (1985) found that when toad bladder epithelial cells were prepared with ibuprofen, subsequent PGE\(_2\) synthesis was enhanced sevenfold, whereas TXB\(_2\) was not.\(^11\) In 1986, Sabatini showed that ibuprofen inhibited the effects of PTH on vasopressin-stimulated water flow in the urinary bladder of toads.\(^106\)

In 1988, Herman and Martínez found that ibuprofen inhibited basal and epinephrine-stimulated PG synthesis in bullfrog lung tissues at 22°C, but not at 5°C.\(^61\) In 1990, Page and Yorio found that the treatment of leopard frogs with ibuprofen at 30 mg/kg/day stimulated mucosal acidification of the abdominal skin that was similar to that found in an animal with chronic metabolic acidosis, and that this effect was inhibited by PGF\(_{2\alpha}\),\(^90\) and this effect was caused by enhanced H⁺ secretion.\(^142\) In 1991, Bhatt et al demonstrated that the addition of certain penetration enhancers increased transportation of ibuprofen through shed snake skin.\(^12\) In 1992, Yakushiji et al showed that when combined with a fluoroquinolone antibiotic, ibuprofen and other NSAIDs inhibited GABA responses in bullfrog sensory neurons.\(^140\) In 1994, Nandi et al found that ibuprofen enhanced histamine-stimulated H⁺ release in the gastric mucosa of frogs.\(^84\) In 2002, Carrasquer demonstrated that ibuprofen altered epithelial transport parameters in the bullfrog cornea.\(^18\)

Toxic effects of ibuprofen have also been documented in reptiles and amphibians. In 2006, Richards and Cole showed that the maximum concentration of ibuprofen detected in surface waters had no significant toxicity, teratogenicity, or growth inhibition in \textit{Xenopus} tadpoles.\(^100\) In 2006, Gladden reported the successful treatment of a South American red-footed tortoise that had ingested 256 mg/kg ibuprofen.\(^42\) In 2014, Veldhoen et al looked at the effects of ibuprofen on bullfrog tadpoles, and found that the LC50 of ibuprofen for this species was 41.5 mg/L, exposure to 15 mg/L altered mRNA transcripts in the liver and disrupted thyroid hormone function, and concentrations as low as 1.5 mg/L altered mRNA in tadpole tailfins.\(^136\) The critical effect environmental contamination concentrations of ibuprofen on aquatic animals, including amphibians, has been calculated.\(^33\)

### Indomethacin

Indomethacin was discovered in 1963. It has been used extensively in research, including studies involving reptiles and amphibians. It also inhibits the motility of polymorphonuclear leukocytes.\(^94\) It is a nonselective COX inhibitor, and many adverse effects have been reported.\(^57,94\)

**Urinary tract:** In 1971, Urakabe et al documented that indomethacin enhanced water permeability when applied on the serosal surface of Japanese common toad bladders in vitro.\(^134\) In 1977, Zusman et al found that indomethacin had no effect on basal water flow in vitro in the bladders of \textit{Bufo} toads, but it increased water flow in response to vasopressin by inhibiting PGE\(_2\) synthesis. It also enhanced cAMP-stimulated water flow, which was determined to be unrelated to its inhibitory effects on PG synthesis.\(^144\) In 1982, Arruda showed that indomethacin significantly decreased the inhibitory effect of high extracellular calcium on vasopressin-stimulated water flow in the toad urinary bladder but not in the turtle bladder, and that it blunts the effect of agents which increase intracellular calcium on water transport, but had no effect on sodium or H⁺ transport.\(^6\) In 1986, Sabatini showed that indomethacin inhibited the effects of PTH on vasopressin-stimulated water flow.\(^106\)

**GI tract:** In 1979, Garner et al found that indomethacin was a potent inhibitor of bicarbonate production by the gastric mucosa of European Frogs, but had a minimal effect on H⁺ secretion.\(^41\) In 1980, Flemstrom found that indomethacin inhibited alkali transport in duodenal mucosa of bullfrogs.\(^34\) In 1986, Rowe et al showed that indomethacin caused no significant changes in potential difference, resistance, or H⁺ secretion on bullfrog gastric mucosa treated with histamine or metiamide (a precursor to cimetidine).\(^104\) In 1994, Nandi et al found that indomethacin did not enhance histamine-stimulated H⁺ release in the gastric mucosa of frogs.\(^84\) Takeuchi et al reported in 1995 that indomethacin caused gastric mucosal ulceration in bullfrogs, even in the presence of a bicarbonate-rich solution.\(^129\)
Reproductive tract: In 1981, Diakow and Nemiroff found that receptive behavior in the female leopard frog was potentiated by treatment with PGE$_2$ and PGF$_{2\alpha}$, and that this effect was blocked by indomethacin. In 1990, Guillette et al showed that indomethacin has an inhibitory effect on oviposition and parturition in oviparous (eastern fence lizards) and viviparous lizards (Yarrow’s spiny lizards). Also in 1990, Jones et al found that indomethacin inhibited ovarian PGE secretion and gonadotropin-induced ovulation in anoles. In 1991, this same group showed that indomethacin-delayed parturition disrupted the normal birth process in viviparous Yarrow’s spiny lizards. In 1995, Chang et al found that indomethacin suppressed ovulation from ovaries obtained during mid-hibernation but not late-hibernation in leopard frogs. In 2006, Jones et al looked at the interactions between uterine tension, PGs, calcium and AVT in the uteri of anoles, and noted that indomethacin blocked the AVT-induced tonic contractions in stretched uteri, and that the interval between contractions was decreased by PGF$_{2\alpha}$ and PGE$_2$, an effect that was also blocked by indomethacin. Ramos et al found that PGF$_{2\alpha}$ increased ovulation induced by a pituitary homogenate in toad ovaries, and that indomethacin produced a significant decrease in this effect.

Endocrine system: In 1981, Delarue et al found that indomethacin caused a marked decrease in the spontaneous production of corticosterone and aldosterone from the interrenal cells from marsh frogs, but did not alter the stimulation of steroidogenesis induced by ACTH. This effect was also documented by Perroteau et al in 1984.

Nervous system: In 1985, Madden and Van der Kloot looked at the effects of indomethacin on transmission at the neuromuscular junctions of frogs, and found that at low doses it irreversibly decreased acetylcholine release, and at high doses it reversibly increased its release. It also decreased the latencies of evoked responses by increasing synaptic delays and increasing nerve action potential conduction times. In 1992, Yakushiji et al showed that when combined with a fluoroquinolone antibiotic, indomethacin and other NSAIDs inhibited GABA responses in bullfrog sensory neurons.

Other effects: In 1976, Hasl et al showed that indomethacin decreased sodium transport across isolated common frog skin in vitro, as well as increasing the sensitivity of the skin to PGE$_1$ at lower doses and decreasing it at higher doses. In 1987, Ferrary et al documented that indomethacin decreased PGI$_2$ and PGE$_2$ synthesis in the frog inner ear. In 1997, Herman et al discovered that indomethacin inhibited clotting in snake blood. In 2001, Stevens et al looked at indomethacin as an analgesic in northern grass frogs, and found that it weak but noticeable analgesic effect using the acetate acid test. In 2002, Bicego et al showed that indomethacin completely blocked the behavioral fever induced by lipopolysaccharides in Roroco toads. In 2010, Staigmiller found that indomethacin had no effect on healthy leopard frog capillaries following a shear stress stimulus. Also in 2010, Priebe found that in capillaries isolated from leopard frogs, the gaps between endothelial cells get smaller when treated with indomethacin, resulting in a decreased flow of fluid out of the capillary. The critical effect environmental contamination concentrations of indomethacin on aquatic animals, including amphibians, has been calculated.

Mefenamic acid

Mefenamic acid was discovered in the early 1970’s. It is a nonselective COX inhibitor that has also been shown to decrease uterine contractions in humans. In 1971, Urakabe et al found that mefenamic acid enhanced the permeability of the toad urinary bladder when applied to the serosal surface in vitro. In 1976, Hall et al showed that mefenamic acid decreased sodium transport across isolated common frog skin in vitro. In 1993, Morales et al found that mefenamic acid caused no appreciable electrophysiological changes in the function of frog cardiac pacemaker cells. In 2004, Ahmad et al looked at the effects of mefenamic acid on the erythrocytes of Uromastyx lizards, and found that it caused a dose-dependent decrease in red blood cell counts, and noted that this drug appears to induce red cell autoantibodies, causing an immune mediated hemolytic anemia-type
In 2005, this same group looked at its effects on blood hemoglobin levels in Uromastyx lizards, and they found significantly higher hemoglobin levels in blood from treated animals when compared to control animals. Also in 2005, this same group looked at the effects of mefenamic acid on osmotic fragility on lacertilian erythrocytes, and found that increased osmotic fragility was observed with increased drug dosage. And in 2006, they looked at its effects on the hematocrits of Uromastyx lizards and found a dose-dependent reduction in mean packed cell volume, and indications of extravascular hemolysis due to destructive changes in the red cell membrane through an autoantibody mechanism.

**Ketoprofen**

Ketoprofen first hit the market in 1972. It is a nonselective COX inhibitor, labeled to treat pain, inflammation, and fever. In 1992, Yakushiji et al showed that when combined with a fluoroquinolone antibiotic, ketoprofen and other NSAIDs inhibited GABA responses in bullfrog sensory neurons. In 2006, Tuttle et al looked at the pharmacokinetics of ketoprofen after IV and IM injections in green iguanas, and they found that it had a 2-compartment disposition when given IV and a 78% systemic absorption when given IM at 2 mg/kg. They recommend a less-frequent dosing interval than is commonly recommended in veterinary formularies (q24h). In 2007, Manire and Norton reported that it could be effectively used in sea turtles at 2 mg/kg IM, but no dosing interval was noted. They did recommend that NSAID’s should only be given for 3-5 days in these animals. In 2014, Pathak et al noted that Indian bullfrogs that were injected with a hypertonic saline solution had increased eye blinking and buccal oscillations in response to pain. They tested multiple analgesic drugs on these frogs, looking for a reduction in these 2 parameters. Even though ketoprofen decreased the number of blinks, it was not significantly different than the controls. In 2015, Yerasi et al used ketoprofen as one of several drugs used to evaluate the frog as an animal model to study the fraction of oral dose absorbed in humans, and found that the absorption rates were comparable. A dose of 2 mg/kg IM, SQ q24h has been recommended for reptiles, but doses up to 4 mg/kg IM q24h have been reported. The critical effect environmental contamination concentrations of ketoprofen on aquatic animals, including amphibians, has been calculated.

**Diclofenac sodium**

Diclofenac was discovered in 1973. It is a non-specific COX inhibitor that may also have some inhibitory effects on LOX. It is primarily used as a topical cream or ophthalmic medication, but oral forms also exist. It has also been used to induce mydriasis in cataract surgery. In 1992, Yakushiji et al showed that when combined with a fluoroquinolone antibiotic, diclofenac and other NSAIDs did not inhibit GABA responses in bullfrog sensory neurons. In 2003, Seebacher and Franklin noted that the heart rates of bearded dragons during heating were significantly faster than during cooling, and that administration of diclofenac blocked this effect, which might be considered an antipyretic effect. In 2004, this same group looked at its effects on heartrate and blood pressure in saltwater crocodiles, and found that it had a similar effect on the heart as in the bearded dragon, but no effect on blood pressure was noted. In 2006, Liu et al looked at this effect in Przewalski’s toadhead agamas, and found that it did not significantly affect heartrate in this species. In 2014, Pathak et al noted that Indian bullfrogs that were injected with a hypertonic saline solution had increased eye blinking and buccal oscillations in response to pain. They tested multiple analgesic drugs on these frogs, looking for a reduction in these 2 parameters. Even though diclofenac sodium decreased the number of blinks, it was not significantly different than the controls. Also in 2014, Mescher amputated a single limb in African clawed froglets at stage 54 and 55 of metamorphosis, when the regenerative ability is initially diminished, and found that topical application of diclofenac at the site of amputation resulted in improved limb regeneration. In 2015, Chae et al found that diclofenac can cause teratogenicity that results in morphological abnormalities in *Xenopus* embryos, but it does not the developmental tissue arrangement during embryogenesis. The critical effect environmental contamination concentrations of diclofenac on aquatic animals, including amphibians, has been calculated.
Naproxen

Naproxen was first marketed as a prescription drug in 1976. It is a nonselective COX inhibitor that is highly protein bound, and linked to GI ulceration, but not cardiovascular disease. In 1977, Zusman et al found that, in the urinary bladders of Bufo toads, naproxen had no effect on basal water flow or on cAMP-stimulated water flow, but it did block PGE synthesis and increased vasopressin-stimulated water flow. Schlondorff et al built on this work, and demonstrated that naproxen significantly enhanced the water flow response of toad bladders to hypertonicity. In 1992, Yakushiji et al showed that when combined with a fluoroquinolone antibiotic, naproxen and other NSAIDs inhibited gamma-aminobutyric acid (GABA) responses in bullfrog sensory neurons. In 1994, Nandi et al found that naproxen did not enhance histamine-stimulated H+ release in the gastric mucosa of frogs. Also in 1994, Vree et al described the glucuronidation of naproxen by red-eared sliders. In 2014, Melvin et al evaluated naproxen as a potential environmental toxin to amphibians. They showed a dose-dependent toxicity of naproxen in striped marsh frog tadpoles, and the effect worsened when it was mixed with carbamazepine and sulfamethoxyzole. In 2015, Yerasi et al used naproxen as one of several drugs used to evaluate the frog as an animal model to study the fraction of oral dose absorbed in humans, and found that the absorption rates were comparable. The critical effect environmental contamination concentrations of naproxen on aquatic animals, including amphibians, has been calculated.

Flunixin meglumine

Flunixin was first introduced into the pharmaceutical market in 1977. It is a potent non-specific COX inhibitor that is highly protein bound. Historically, flunixin meglumine has been used extensively in reptiles and amphibians at doses ranging from 0.1-2 mg/kg IV, IM q12-24h in reptiles and 0.1-1 mg/kg IV, IM q12-24 in amphibians, but little research has been done on the use of this NSAID in these species. Morales et al found that flunixin caused a dose-dependent decrease and eventual cessation in the electrophysiological function of frog cardiac pacemaker cells. In 1996, Terril-Robb et al looked at the analgesic effects of flunixin in leopard frogs, and found that 25 mg/kg provided good analgesia for 2 to 4 hours. In 2011, Coble et al determined that 25 mg/kg administered into the dorsal lymph sac of African-clawed frogs provided longer and more effective analgesia compared to controls and to frogs treated with morphine, xylazine, or meloxicam. However, one frog in this treatment group did die afterward, and renal lesions were noted on histopathology.

Piroxicam

Piroxicam is an NSAID in the oxicam class that was introduced in 1977. It is a non-selective COX inhibitor, and in addition to its use in treating pain, inflammation, and pyrexia, it is also noted to have antineoplastic effects, particularly in the treatment of transitional cell carcinomas in dogs and cats. In 1992, Yakushiji et al showed that when combined with a fluoroquinolone antibiotic, piroxicam and other NSAIDs did not inhibit GABA responses in bullfrog sensory neurons. In 2014, Pathak et al found that the number of eye blinks and buccal oscillations increased with a painful stimulus in African clawed frogs, and that piroxicam decreased this response, but was not significantly different from controls. Its use as an antineoplastic drug in reptiles and amphibians has not been reported. The critical effect environmental contamination concentrations of piroxicam on aquatic animals, including amphibians, has been calculated.

Meclofenamic acid (meclofenamate)

Meclofenamic acid was introduced in 1980 as an NSAID for horses. It is a nonselective COX inhibitor. Zusman et al found that, in the urinary bladders of Bufo toads, meclofenamic acid had no effect on basal water flow or on cAMP-stimulated water flow, but it did block PGE synthesis and increased vasopressin-stimulated...
water flow. In 1980, Schlondorff et al built on this work, and demonstrated that meclofenamate significantly enhanced the water flow response of toad bladders to hypertonicity. When applied to the corneas of Bufo toads in vitro, Bentley and McGahan found that meclofenamic acid inhibited the flux of chloride toward the tear surface. Richter et al showed that meclofenamic acid had a similar effect in lung tissue isolated from African clawed frogs. In 1985, McGahan et al showed that melittin, a compound isolated from bee venom, increased the short-circuit current across the skin and corneas of Bufo toads, and that this effect is inhibited by meclofenamic acid. In 1986, Miller and Vanhoutte noted that in the isolated descending aortas from turtles, caymans, and bullfrogs, acetylcholine caused contraction-dependent relaxation of aortas in caymans and bullfrogs and contraction of aortas from turtles, and that meclofenamate did not inhibit this response. Also in 1986, Duranti et al found that meclofenamate inhibited acid secretion through the skin of edible frogs.

**Carprofen**

Carprofen was introduced to the human market in 1988, and the veterinary market in 1996. Unlike its predecessors, it has more COX-2 specificity, and is more sparing of COX-1. As a result, side effects tend to be fewer and much less severe. There are few studies looking at carprofen in reptiles and amphibians, but many reports of its empirical use in these species. In 1994, Nandi et al found that carprofen did not enhance histamine-stimulated H+ release in the gastric mucosa of frogs. In 2007, Trnkova et al examined the effects of carprofen on blood profile parameters in green iguanas, and found that animals treated with carprofen had a decreased hemoglobin and hematocrit, and an increase in azurophils compared to controls. They also had significantly higher AST and ALT activity. Empirically, carprofen has been used in a Greek tortoise at 2 mg/kg IM, in a bluetongue skink at 4 mg/kg IM q24h for 5 treatments, in a green sea turtle at 1.5 mg/kg PO q48h for 4 months, in a White’s tree frog at 4 mg/kg IM, in red-eared sliders at 2 mg/kg IM and 4 mg/kg IM, in a black water monitor at 3.33 mg/kg SQ, followed by 4 mg/kg PO q24h for 14 days, in a diamond python at 2 mg/kg IM, and in a monocellate cobra at 2 mg/kg IM q24h for 3 treatments. No side effects attributed to carprofen use were documented in any of these case reports, including the monocellate cobra, which was being surgically treated for renal gout. Doses at 1-4 mg/kg IM, IV, SQ, or PO q24-72h have been reported for reptiles.

**Flurbiprofen**

Flurbiprofen was introduced in 1988. Although an oral formulation has been utilized in humans, the topical ophthalmic formulation is typically used in veterinary medicine. It is a nonselective COX inhibitor that has also been shown to inhibit miosis. There are few reports of its use in reptiles and amphibians. De Voe et al used it topically q12-24h to manage conjunctivitis in an eastern box turtle infected with ranavirus. Dolinski et al used it topically q24h to treat a systemic fungal infection that also affected the eyes of a plains garter snake.

**Ketorolac**

Ketorolac was introduced in 1989. Oral, parenteral, and ophthalmic human-label formulations are available. Ketorolac is a nonspecific COX inhibitor that is similar to aspirin, except without significantly affecting platelet function. In 1998, Henson and Lewbart looked at ketorolac for management of post-operative pain in injured wild turtles, and found that turtles that received the drug following shell fracture repair began eating much sooner than controls. In 2001, Stevens et al looked at ketorolac as an analgesic in northern grass frogs, and found that it weak but noticeable analgesic effect using the acetic acid test. The critical effect environmental contamination concentrations of ketorolac on aquatic animals, including amphibians, has been calculated.
Etodolac

Etodolac was introduced in 1991. It is considered to be a COX-1 sparing drug rather than a COX-2 selective drug. There is only one published report of its use in reptiles. In 2010, O’Shea and Ball reported its use in a Komodo dragon at 5 mg/kg PO q72h for 30 days. Even though it was given concurrently with 4 mg/kg ketoprofen IM q24h, no side effects were reported.

Meloxicam

Meloxicam was first introduced in 1995, although it was several years later before it was available in the US. It is considered to be COX-2 preferential but not COX-2 specific, because its specificity is diminished at higher dosages. Due to its safety, ease of administration, and performance record, meloxicam has become the NSAID of choice in most exotic species.

Reptiles: Divers et al looked at the pharmacokinetics of meloxicam in green iguanas, and found that the administration of meloxicam at 0.2 mg/kg IV or PO would result in plasma concentrations >0.1 µg/ml for approximately 24 hours, and that oral overdose at 10-50 times the recommended dose for 2 weeks produced very high terminal plasma levels, but no evidence of toxicity based on hematology, biochemistry, and histopathology. In 2007, Trnkova et al examined the effects of meloxicam on blood profile parameters in green iguanas, and found that animals treated with meloxicam had increased ALT activity and a decrease in blood calcium concentrations. In 2008, Olesen et al looked at the effects of perioperative administration of meloxicam on the physiologic responses to surgery in ball pythons, and found that a dose of 0.3 mg/kg IM neither decreased the physiologic stress response nor provided an analgesic effect to treated ball pythons compared to controls. Response to therapy was based on hematological analysis, assays of plasma catecholamines and cortisol, changes in blood pressure and heart rate, and behavioral observations. In 2009, Rojo-Solis et al looked at the pharmacokinetics of meloxicam administered IV, IM, or PO to red-eared sliders, and found that after IV administration of 0.22 mg/kg, plasma clearance was rapid, resulting in an elimination half-life of 7.57 hours. Administration of 0.5 mg/kg IM and PO resulted in a rapid absorption via both routes, but IM administration showed significantly higher bioavailability and maximum concentrations than PO administration, and subsequently more predictable clinical pharmacokinetic behavior; PO administration also showed marked individual variability. In 2015, Olimpia et al investigated the pharmacokinetics of meloxicam administered at 0.1 mg/kg IM and IV in loggerhead sea turtles, and noted a rapid elimination time, with the plasma drug concentration dropping below analytical limits within 8 hours, and concluded that this dose is inadequate for this species. Also in 2015, Deli et al looked at the pharmacokinetics of meloxicam after a single dose of 0.2 mg/kg IM, PO, and ICe in red-eared sliders, and found that after IV and ICe administration, plasma drug concentrations were 10 times that of PO administration. Doses ranging from 0.1-0.5 mg/kg IV, IM, SQ, or PO q24-48h have been recommended.

Amphibians: In 2011, Minter et al looked at the effects of IM meloxicam on PGE$_2$ in bullfrogs following tissue trauma by a punch biopsy, and found that 0.1 mg/kg IM q24h was effective in suppressing PGE$_2$ levels in this species. In 2011, Coble et al determined that 0.2 mg/kg meloxicam administered into the dorsal lymph sac of African-clawed frogs provided analgesia similar to morphine and xylazine, but significantly less than flunixin meglumine. Wright recommends a dose of 0.05-0.1 mg/kg PO q24-72h for the treatment of corneal lipidosis, but doses up 0.4 mg/kg IM, SQ, or ICe have been recommended. The critical effect environmental contamination concentrations of meloxicam on aquatic animals, including amphibians, has been calculated.
Celecoxib

Celecoxib is a selective inhibitor of COX-2. It was introduced to the human market in 1995. The most common veterinary usage is for management of inflammation in birds suffering from PDD. In 2008, Sharma and Suresh looked at its effects on tail regeneration in northern house geckos, and found that animals treated with celecoxib had delayed tail regrowth. However, In 2014, Mescher amputated a single limb in African clawed froglets at stage 54 and 55 of metamorphosis, when the regenerative ability is initially diminished, and found that topical application of celecoxib at the site of amputation resulted in improved limb regeneration and digital patterning. The critical effect environmental contamination concentrations of celecoxib on aquatic animals, including amphibians, has been calculated.

Rofecoxib

Rofecoxib was discovered in 1995, and approved for human use in 1999. It is a selective COX-2 inhibitor. There is limited information about its use in amphibians. In 2002, Carrasquer demonstrated that rofecoxib altered epithelial transport parameters in the bullfrog cornea. In 2006, Zelarayán et al reported that rofecoxib inhibited frog pituitary meiosis resumption in *Bufo arenarum* follicles treated with hCG and PGE1. The critical effect environmental contamination concentrations of rofecoxib on aquatic animals, including amphibians, has been calculated.

Etoricoxib

Etoricoxib is a COX-2 selective inhibitor that was introduced to the human market in 1999. In 2008, Sharma and Suresh looked at its effects on tail regeneration in northern house geckos, and found that animals treated with etoricoxib had delayed tail regrowth, with a 71% reduction in growth rate during the 2-12 mm stage and a 54% reduction during the 12-24 mm stage of regeneration. In 2015, Narayanan found that etoricoxib at 50 mg/kg inhibited PGE2- and FGF2-induced tail regeneration in northern house geckos. The critical effect environmental contamination concentrations of etoricoxib on aquatic animals, including amphibians, has been calculated.

Other NSAIDs utilized in veterinary medicine

Bromfenac, Deracoxib, Fenclofenac, Firocoxib, Mavacoxib, Napafenac, Robenacoxib, Suprofen, Tepoxaline, and Tolfenamic acid have been utilized in veterinary patients. No information about the use of these drugs in reptiles or amphibians could be found.

Key References

Below are select references cited in the text. A full reference list is available upon request from Dr. Hannon at hannondvm@msn.com.


