Making informed decisions on NSAIDS: COX story uncovered

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The veterinary profession continues to benefit from the increasing number of NSAIDs available for pain management in small animal patients.

As patients live longer and new NSAIDs become available, veterinarians have to make decisions about NSAIDs daily.

The availability of a greater range of NSAIDs can only benefit our patients, but it may also cause confusion when the veterinarian needs to make an informed and evidence-based decision about which NSAID is best for each individual animal.

This confusion is exacerbated by a plethora of marketing material, with competing claims made for the superiority of one drug over another. The choice of NSAID is also increasingly likely to be scrutinised by the discerning owner, who is expecting the very best care for his or her pet.

It is important to recognise that individual responses to NSAIDs vary, and no single NSAID will be suitable for all patients. However, an understanding of these drugs'clinical pharmacology, and the basis on which claims are made by drug companies, should assist the clinician in his or her choice of drug for the individual patient.

How NSAIDs work

Advancements in the development of NSAIDs have revolutionised pain relief for the veterinary patient. Acute and chronic pain can now be effectively managed for conditions such as trauma, osteoarthritis and neoplasia. The pre and postoperative care we can offer our surgical patients has also been transformed with the use of newer NSAIDs.

The mode of action of these drugs explains their effectiveness and why their development can benefit patients. However, there are differences between NSAIDs; for the clinician to choose the appropriate NSAID for an individual patient, an understanding of each of their modes of action is important.

NSAIDs act by inhibiting the production of several inflammatory mediators produced in the inflammatory pathway (shown in Figure 1).

As the pathway demonstrates, NSAIDs inhibit the production of prostaglandins and thromboxane via inhibition of the enzyme cyclo-oxygenase (COX). Some NSAIDs, such as tepoxalin, may inhibit both COX and lipoxygenase (LOX).

Prostaglandins and leukotrienes do not cause pain directly, but potentiate the effects of other inflammatory mediators that do cause pain, such as bradykinin, serotonin and histamine (a phenomenon known as hyperalgesia). They are also potent pyretic agents and dilators of the vascular smooth muscle, leading to vasodilation and oedema during acute inflammation.

NSAIDs inhibit the production of prostaglandins and leukotrienes, which explains why they have anti-inflammatory, anti-pyretic and analgesic effects.

The COX story

Marketing literature related to NSAID products will often use claims related to COX-1 and COX-2 inhibition, most of which are used to sell the benefits of the products. So what is the COX story all about, and how can we better understand the science behind the terminology?

There are two main variants of the COX enzyme, COX-1 and COX-2 (Figure 2). A third variant (COX-3) is thought to play a role in the central perception of pain.

Arachidonic acid cascade

COX-1 (the physiological enzyme) is involved in the production of prostaglandins important in the physiological modulation of function, especially the gut mucosal barrier and intra-renal perfusion when renal blood flow is reduced.

COX-2 (the pathological enzyme) is activated and released by tissue damage, bacterial lipopolysaccharide, cytokines, growth factors and inflammation.

The current thinking is that the two main isoenzymes do not have completely separate roles and there is some overlap in the function of COX-1 and COX-2. Prostaglandins produced by COX-1 may have a role in inflammation. COX-2 may produce some physiological prostaglandins, which could, for example, aid healing of preexisting gastric ulcers. COX-2 also plays a homeostatic role within certain organs, including the ovary and kidney.

Gastric ulceration

Prostaglandins produced by COX-1, predominately PGI-2 (prostacyclin) and PGE-2, play an essential role in many body functions, including maintaining the integrity of the barrier protecting the gastric mucosa from damage by gastric acid. Prostaglandins protect the gastric mucosa by:

- decreasing the volume, acidity and pepsin content of gastric secretions;
- stimulating bicarbonate secretion by epithelial cells;
- producing vasodilation in gastric mucosa;
- increasing gastric and small intestinal mucus production;
- stimulating turnover and repair of gastrointestinal epithelial cells;and
- increasing the movement of water and electrolytes in the small intestine.

All NSAIDs have the potential to cause gastric ulceration (Figure 3) by inhibiting prostaglandins. The only exception appears to be paracetamol, as it only inhibits prostaglandin synthesis centrally.

Dogs appear particularly sensitive to NSAIDs'gastrointestinal side effects compared to other species, possibly as a result of increased enterohepatic recycling of the drugs in this species.

Although many COX-1 selective drugs are more ulcerogenic than COX-2 preferential or selective drugs, the relationship between COX-1 inhibition and the risk of gastric ulceration is complex – gastrointestinal toxicity is not entirely due to the inhibition of physiologically important prostaglandins.

The evidence for this is that some NSAIDs that inhibit gastric mucosal prostaglandin production or concentration are not overly ulcerogenic.

In addition, preferential and highly selective COX-2 inhibitors appear to have reduced gastrointestinal toxicity overall, but do – on occasion – have ulcers reported as an adverse effect. Other factors that may influence the safety of NSAIDs involve acidity of the pro-drug, plasma half-life, degree of enterohepatic recycling and the potential for polymorphism in metabolism (such as the genetically determined difference in drug metabolism between individuals).

Regardless of the mechanism, however, the ulcerogenic potential of NSAIDs is increased by concurrent corticosteroid treatment, a practice for which there is little rational basis. If, for some reason, a single dose of corticosteroid and NSAID is regarded as essential, co-administration of a protective agent, such as misoprostol, should be considered and the patient monitored closely.

Dehydration, hypovolaemic shock and disruption to normal gastrointestinal blood flow also increase the ulcerogenic potential of NSAIDs. The use of NSAIDs in the management of a patient with hypovolemic shock secondary to trauma has no rational basis and is clinically insupportable, particularly when such drugs are used concurrently with corticosteroids.

Renal toxicity

Renal toxicity is a potential side effect associated with NSAIDs and is caused by reduced renal blood flow and glomerular filtration rate secondary to inhibition of renal prostaglandin synthesis.

Renal prostaglandins are involved in maintaining renal blood flow via their vasodilatory actions. In a healthy, wellhydrated animal, reduced renal prostaglandin production is of little consequence.

However, significant renal toxicity can result if an animal is volume depleted, is avidly retaining sodium (for example, in congestive heart failure or hepatic cirrhosis) or has pre-existing renal insufficiency. Although prostaglandins produced by COX-1 play a predominant role in renal protection under these circumstances, relative COX-2 selectivity may not remove the risk of renal side effects as COX-2 also has a constitutive physiological role in renal function.

The potential for renal toxicity to occur in a volume-depleted animal is a further reason why NSAIDs should not be administered to any animal in shock posttrauma, or to any animal that may have significant gastrointestinal disease resulting in dehydration and volume depletion.

Prolonged bleeding times

Prolongation of bleeding times due to the inhibition of platelet thromboxane production can occur after the administration of NSAIDs. Thromboxane is a potent vasoconstrictor and stimulus for platelet aggregation, and the reduced vasoconstriction and platelet aggregation that occurs may be significant in patients with bleeding tendencies or may complicate surgical procedures.

The older NSAIDs, which significantly inhibit COX-1, carry a great risk of this side effect, especially aspirin and phenylbutazone, where COX inhibition is irreversible and, therefore, persists for the life of the platelet.

Studies with more COX-2-selective drugs, such as carprofen, deracoxib and firocoxib, have not shown prolongation of bleeding time – even at high doses.

Can NSAID safety be measured?

It makes sense that the safety of an NSAID is measured according to the relative ability of that drug to inhibit COX-1 and COX-2. However, there are pitfalls when attempting to interpret data related to COX-1 and COX-2 inhibition.

COX-1: COX-2 ratios

The COX-1: COX-2 ratio is often used as a measure of an NSAID’s relative ability to inhibit COX-1 and COX-2. Ratios can vary between drugs and, in part, explains why some NSAIDs are potentially more toxic than others. However, care should be taken when interpreting results of individual

NSAIDs, as the relative COX-2 selectivity of a drug will be influenced by the assay chosen, the tissue type and the species used. Some figures may be based on different assays used in different tissues from various species, resulting in variable figures (even for the same drug) that further confuse the clinician. The gold standard (and only relevant assay system) when assessing the relative selectivity of different drugs is the whole-blood assay in the species of interest. The same drug in different species may vary in potency and relative selectivity for COX-1 and COX-2. For example, in dogs, carprofen is COX-2 preferential or selective;in horses, it is nonselective;and in cats it is COX-2 selective. In humans, carprofen is COX-1 selective.

IC_{50} values

IC_{50} values (concentration giving 50 per cent inhibition of COX) for COX-1 and COX-2 are often reported in studies and marketing data. A COX-1: COX-2 $IC5_0$ ratio that is less than one (1) indicates that a drug is selective for COX-2. The IC_{50}COX-1: IC_{50}COX-2 ratio is, therefore, used to express the relative safety of a drug – the higher the ratio, the more COX-2 preferential the drug.

However, it is more relevant to look at the ratio that reflects the clinically desirable degree of inhibition for each enzyme. This is believed to be 20 per cent or less for COX-1 inhibition (to avoid side effects related to inhibition of physiological prostaglandins) and 80 per cent or more for COX-2 inhibition (to achieve therapeutic efficacy).

NSAID types

Traditional NSAIDs (Figure 4) inhibit both COX-1 and COX-2, which treats the pain and inflammation caused by COX-2, but also inhibits the physiological effects of COX-1.

The unwanted side effects of these drugs often mean that an effective pain-relieving dose cannot be used in the long term.

• **COX-2 preferential drugs** (Figure 5)

Although the terminology sounds impressive, it is important to be aware that the most clinically relevant result that can be obtained from a drug manufacturer is the percentage of COX-1 that is inhibited when 80 to 100 per cent of COX-2 is inhibited. Even COX-2 preferential drugs, such as carprofen and meloxicam, inhibit greater than 20 per cent of COX-1 when used at clinically relevant doses that inhibit 80 per cent or more of COX-2. As a result, side effects relating to COX-1 inhibition are still possible, although the risk is certainly less than with the older, nonselective drugs such as aspirin, phenylbutazone and ketoprofen.

• **COX-2 selective or specific drugs** (**coxibs;** Figure 6)

Coxibs are the next generation of NSAIDs. COX-2-specific (“coxib”) drugs, such as firocoxib, are

COX-2 selective. COX-1 inhibition by firocoxib is only three per cent when COX-2 is inhibited by 100 per cent, which is a highly desirable degree of inhibition for each enzyme.

The COX-1: COX-2 selectivity ratio is also impressive when compared to carprofen and meloxicam. When measured via the gold-standard “canine whole blood assay”, firocoxib was 380 times more selective for COX-2 than COX-1 when compared to meloxicam and carprofen, which were 10 times and seven times selective respectively. However, it remains to be seen whether a meaningful difference in adverse events will be associated with the greater COX-2 selectivity. Appropriate case selection and monitoring remains a requirement for the use of any NSAID.

NSAIDs’effects on vascular disease

Some internet-savvy and wellread owners may express concerns over the use of COX-2–selective drugs, as detrimental effects have been reported within the human field of medicine. However, it should be noted that these effects cannot be extrapolated to dogs.

COX-2 has a role in sustaining prostacyclin production, which causes vasodilation and opposes the platelet-aggregating effects of thromboxane. Therefore, inhibition of COX-2 by only the truly COX-2-selective drugs (coxibs) can allow the plateletaggregating effect of thromboxane (synthesised by COX-1) to go unchecked. This can be deleterious in human patients with atherosclerotic disease, and has been shown to increase the risk of cardiovascular (myocardial infarctions and pulmonary emboli) and stroke incidents. As a result of these concerns, some coxib drugs have been removed from the human market.

In dogs and cats, atherosclerotic cardiac disease does not occur. There are differences between the species in lipoprotein profiles, and the canine heart has a greater degree of collateral coronary artery circulation than in man. As a result, there does not appear to be any increased cardiac risk factors when coxibs are used in this species.

Dual COX/LOX inhibitors

Tepoxalin inhibits COX-1 and COX-2 to the same degree or may even inhibit COX-1 preferentially. It inhibits lipoxygenase for a short period of time during the 24-hour period, which contributes to its anti-inflammatory effect – although the degree to which this is clinically relevant (due to the short time period) is debated.

NSAID choice

Patients need to be considered on an individual basis, and one particular NSAID is unlikely to fulfil the requirements of every patient. Choice should be made according to some of the following factors.

- What type of pain is involved – acute, chronic, visceral or somatic?
- Can the patient be easily medicated?
- Is the patient compromised in any way?
- Are other drugs being used concurrently, such as corticosteroids and ACE-inhibitors?
- Have NSAIDs been used previously and how effective were they? Were any side effects demonstrated?

Obviously, safety and efficacy are the keys to a desirable NSAID. The drug should have been specifically developed to achieve optimal inhibition of COX-2 without compromising the physiological functions of COX-1 at therapeutic doses. As previously discussed, the data demonstrating these characteristics should be carefully interpreted.

In addition, there are some basic guidelines to follow when considering the safe use of any NSAIDs.

- Patients should be well hydrated and have no conditions that affect their gut or renal blood flow.
- NSAIDs should be avoided in hepatic disease. If this is not possible, the dose interval should be increased (in effect, the same dose but given less frequently).
- NSAIDs should be avoided when renal blood flow is reduced, as there is a risk it may be reduced further, or when pathological sodium retention is present, such as in patients with nephrotic syndrome, cardiac failure and cirrhotic hepatic disease.
- Care should be taken when using NSAIDs alongside ACEinhibitors as both prostaglandins and angiotensin-II are important in protecting intrarenal perfusion. These patients are at greater risk of renal toxicity should their renal perfusion become compromised by, for example, dehydration or exacerbation of their cardiac disease. Therefore, it is vital that clients be informed that veterinary advice should be sought immediately should there be a change in the patient’s clinical status. If there are any doubts, it would be prudent to cease providing the NSAID (rather than the ACEinhibitor) until hydration and renal perfusion is fully restored.

Conclusion

With a large number of available NSAIDs now available, and new treatments coming on to the market, it is hoped the reader will now be well-equipped to ask appropriate questions of drug manufacturers and make a suitable choice for his or her individual patients.

• References available upon request to the editor.

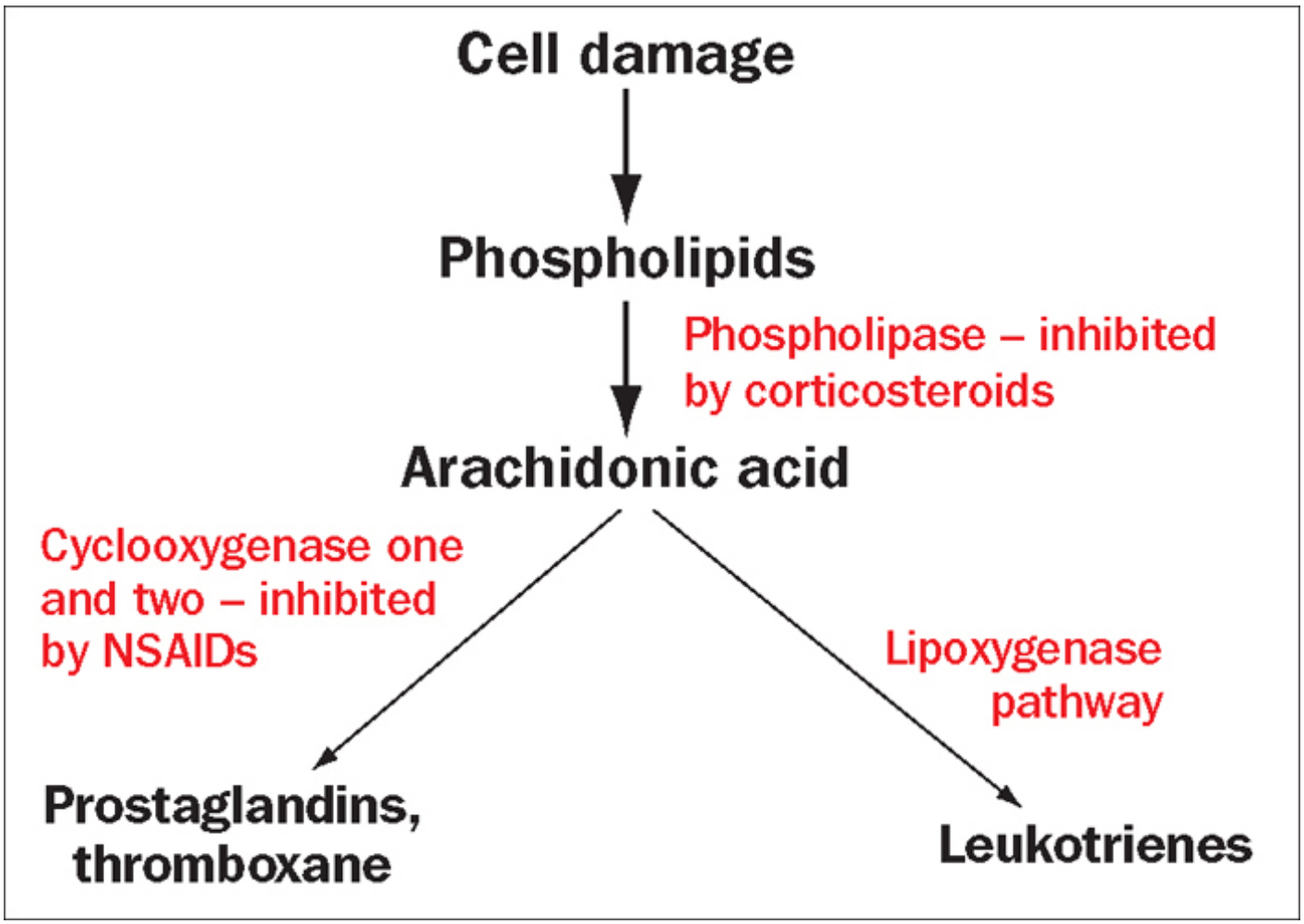

Figure 1. The inflammatory pathway.

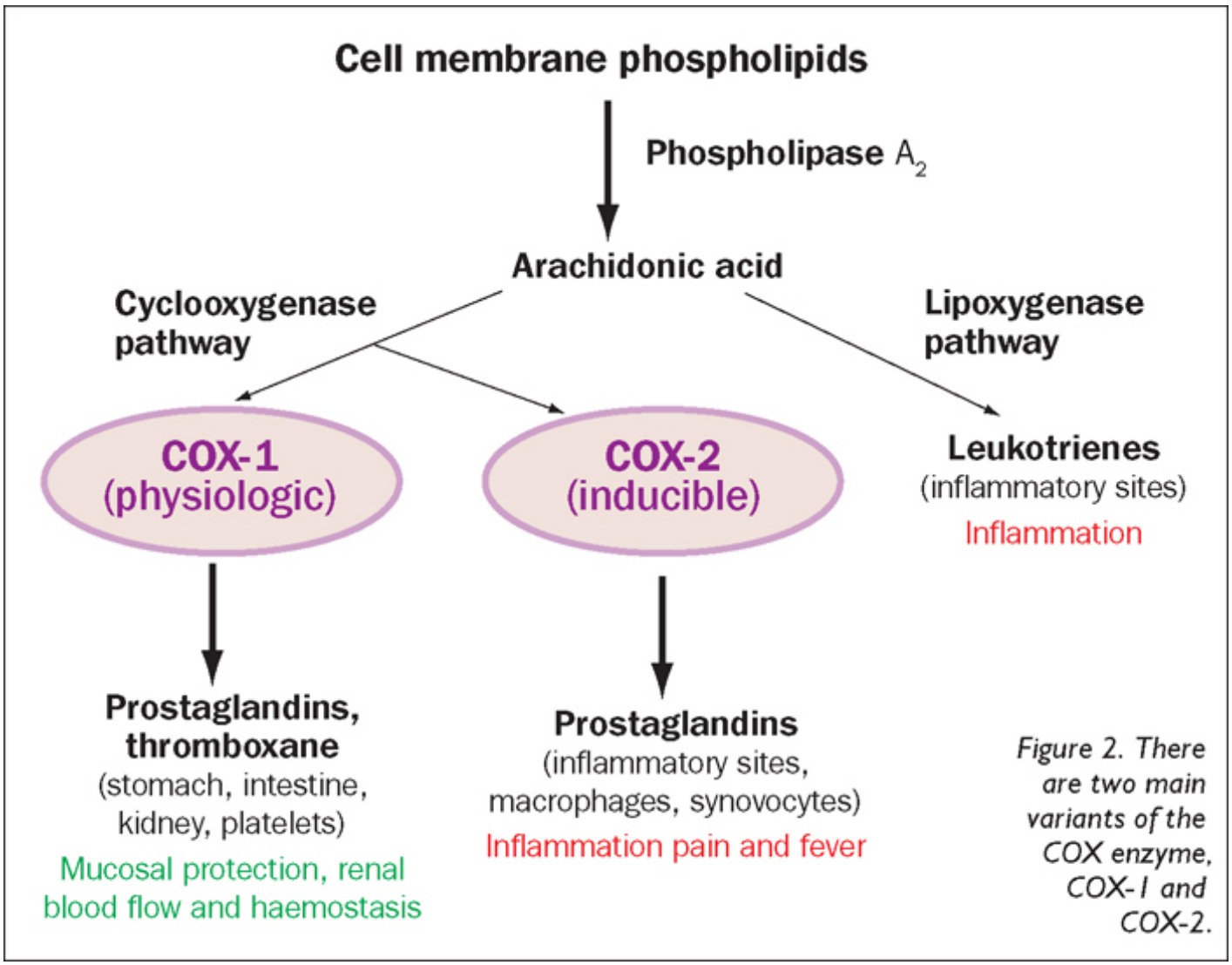

Figure 2. There are two main variants of the COX enzyme, COX-1 and COX-2.

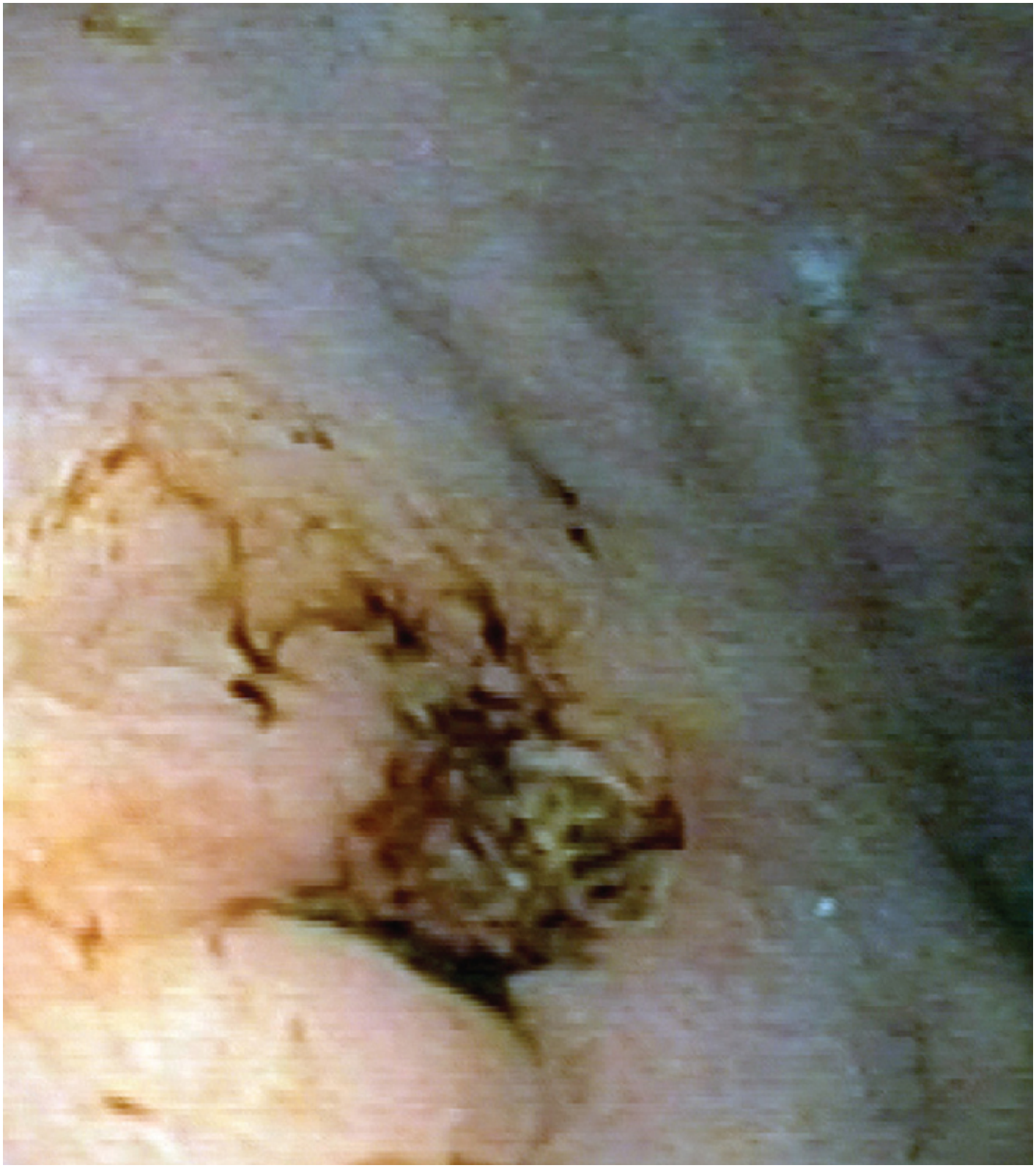

Figure 3. A gastric ulcer.

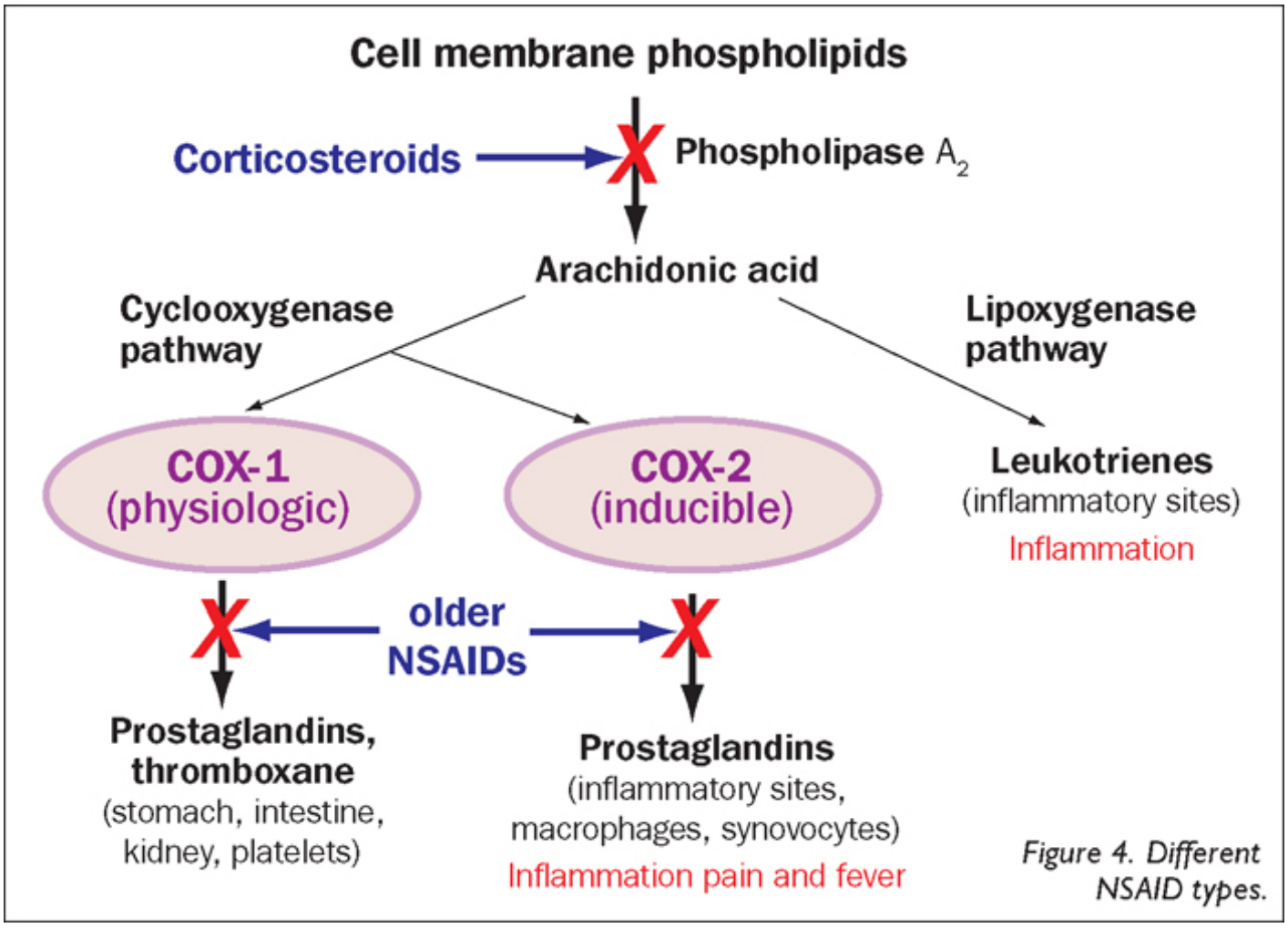

Figure 4. Different NSAID types.

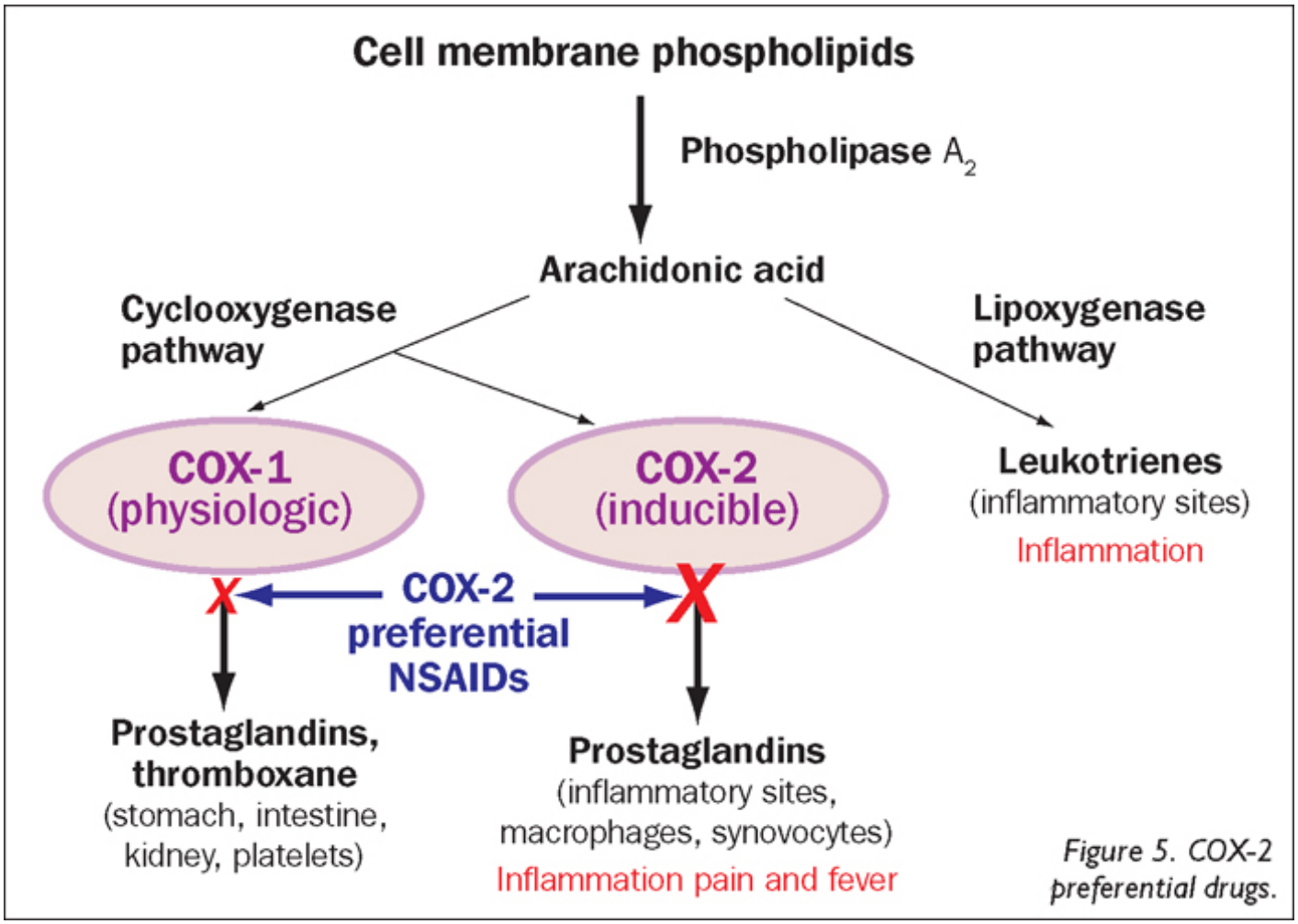

Figure 5. COX-2 preferential drugs.

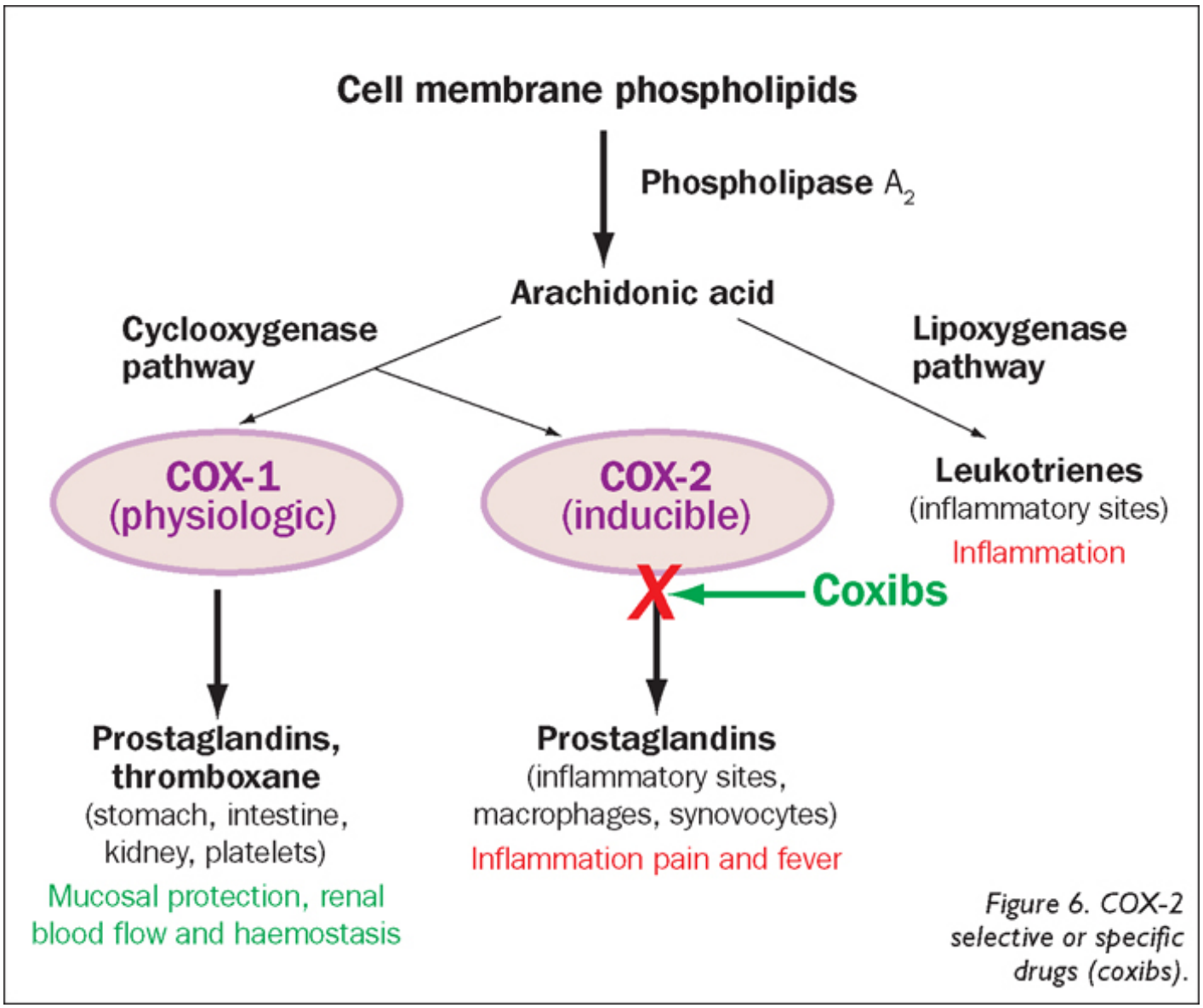

Figure 6. COX-2 selective or specific drugs (coxibs).

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