The use of NSAIDs to treat inflammation, pain and fever

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Inflammation, pain and fever are symptoms that frequently occur together. However the use of anti-inflammatory, analgesic and antipyretic drugs in farm practice is low for reasons that include cost, fear of residues and tradition.

Regarding cost, we must bear in mind that animals in pain and fever are likely to be less productive because they diminish feed consumption. For instance, chronic pain changes an animal's metabolism adversely. This is likely to cause stress which will reduce milk yield and fertility in sows. Furthermore, the great majority of diseases present on farm are related to inflammation (for example Actinobacillus pleuropneumoniae, Mycoplasma sp., Bordetella bronchiseptica, Pasteurella sp., PRRS, hog cholera, and FMD among others). So the cost saving derived from not using analgesic and anti-inflammatory drugs is not so obvious.

Concerning residues, some drugs such as last-generation NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) usually show relatively short withholding times, so they should not be a problem. Furthermore, this kind of pharmaceutical is often used together with antibiotics, which also present their own withdrawal time requirements. NSAIDs may help antibiotics to act quicker as they facilitate antibiotic action on target tissue. So the use of NSAIDs is even more justified when antibiotic treatment is performed.

With respect to tradition, although the treatment of inflammation, pain and fever in farm animals has never been considered a priority, future trends indicate that social pressure will force the increased use of analgesics, especially in routine husbandry procedures such as dehorning and castration, and in painful diseases such as lameness and mastitis. Animal welfare will also be used as a trade barrier in imports-exports worldwide.

So, although valid reasons for not using NSAIDs include cost and concerns about residues, which ultimately also means cost, a point often overlooked is that pain, inflammation and fever are likely to reduce productivity.

Table 1. Activity of several NSAIDs on COX isoenzymes.

Non-preferential COX-2 inhibitors	Preferential COX-2 inhibitor
Ketoprofen	Meloxicam
Carprofen	Tolfenamic acid
Flunixin meglumine	

Use of NSAIDs

During recent years the use of steroidal anti-inflammatory drugs – such as dexamethasone, betamethasone, and prednisolone – has been discarded in favour of NSAIDs.

This is due to the fact that although steroidal drugs show a powerful activity that can quickly reduce inflammation and pain, they also present high potential side effects. They are usually prescribed in low doses or for short durations.

Chronic or inappropriate use of corticosteroids (also named steroidal anti-inflammatory drugs) can cause life-threatening hormonal and metabolic changes.

Corticosteroids suppress immune response. Animals receiving systemic corticosteroids may be more susceptible to bacterial or viral infections. Systemic corticosteroids can mask signs of infection, such as an elevated temperature. They are also contraindicated in patients with systemic fungal infections. Its use in young animals may both cause immune suppression and GI ulcers.

Corticosteroids should be avoided during pregnancy and lactation unless the benefits outweigh the risks. Large doses in early pregnancy may be teratogenic in some species. In the last half of gestation they have the potential to induce abortions, especially in ruminants.

The incidence of side effects – either annoying or more serious – increases as the potency of the corticosteroid increases because their anti-inflammatory effects are inherently linked with suppression of the immune response and associated consequences.

On the other hand, NSAIDs have the potential to relieve pain and inflammation without the immunosuppressive and metabolic side effects associated with corticosteroids.

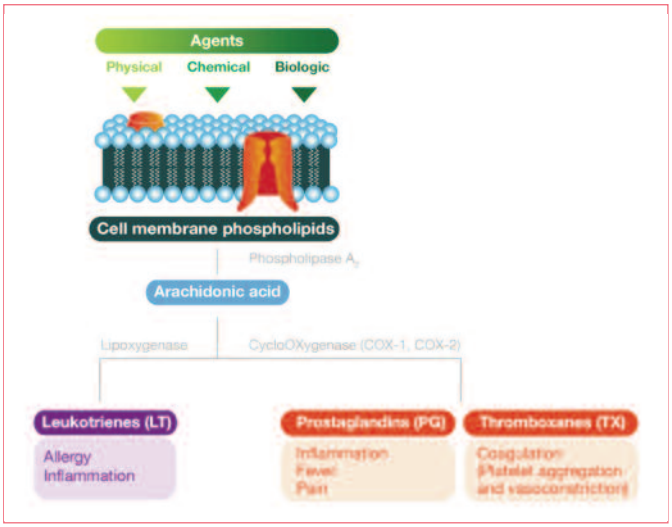

Fig. 1. Arachidonic acid metabolism and formation of inflammatory mediators (PGs, TXs and LTs).

Classification of NSAIDs

There are several types of NSAIDs currently on the market. They are usually differentiated by their mechanism of action. Depending upon which CycloOXygenase (COX) iseoenzyme they act on, we can differentiate between:

- Non-selective cyclooxygenase inhibitors: ketoprofen, carprofen and flunixin meglumine.
- Preferential cyclooxygenase-2 (COX-2) inhibitors (this means that they preferentially inhibit COX-2 over COX-1): meloxicam and tolfenamic acid.

For better understanding of this classification it is important to have a general idea about how NSAIDs work. Although the mechanism of inflammation, pain and fever is a very complicated one that would need an entire article just to be resumed, we will try here to give the main key points.

Everything starts when cells are attacked by physical, chemical or biologic agents (for example temperature, infections). The cellular membrane is broken and arachidonic acid is freed from the phospholipids that form the cellular membrane by the enzyme phospholipase A2 (PLA2). Arachidonic acid can be transformed in different substances which have different effects depending on which enzyme acts on it: cyclooxygenase (COX) or lipoxygenase (LOX).

In the case that cyclooxygenase is the enzyme which acts upon arachidonic acid, prostaglandins (PGs) and thromboxanes (TXs) are the substances synthesized. PGs have a role in inflammation, pain and fever mechanisms while TXs participate in the coagulation process.

In the case that lipoxygenase is the enzyme which acts upon arachidonic acid, leukotriens (LTs) are the substances synthesized. LTs have a role in inflammation and allergy mechanisms.

The three types of substances (PGs, TXs and LTs) are considered inflammatory mediators (Fig. 1).

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The great majority of NSAIDs only act on COX isoenzyme while corticosteroids act on the enzyme phospholipase A2 (Fig. 2). That is probably the reason why corticosteroids are so potent and also show more severe adverse effects.

Differences among NSAIDs

There are several types of COX isoenzymes, although the most common ones are COX-1 and COX-2. Initially it was thought that COX-2 was the 'bad' enzyme while COX-1 was the 'good' enzyme, so research on NSAIDs was focused on preferentially inhibiting COX-2 isoenzyme in order to decrease possible adverse effects. Tolfenamic acid and meloxicam would be included within this group of NSAIDs. However, later on it has been seen that there is accumulating evidence that COX-1 and COX-2 have overlapping actions and that both isoforms are involved in homoeostasis processes, just as both are modulators of inflammatory reactions. Non-preferential COX-2 inhibitors – such as ketoprofen, carprofen and flunixin meglumine – have action on both COX isoenzymes.

In human medicine, new dual 5-LOX/COX inhibitors are now being studied as potential new drugs to treat the inflammatory processes. Such combined inhibition avoids some of the disadvantages of selective COX-2 inhibitors and spares the gastrointestinal mucosa. This approach is currently considered as the future trends in veterinary medicine. Ketoprofen and carprofen are NSAIDs that also act on LOX isoenzyme.

Contrary to ketoprofen, carprofen and flunixin meglumine are not used in human medicine. Carprofen was used in humans for 10 years but later it was found to have a weak effect and it disappeared from the market.

Conclusions

The great majority of diseases present in farms are related to inflammation. Inflammation, pain and fever are symptoms that are likely to reduce productivity.

Modern NSAIDs present very few residues and thus very short or non-existent withdrawal times. Future trends indicate that social pressure will force an increased use of analgesics, especially in routine husbandry procedures such as dehorning and castration, and in painful diseases such as lameness and mastitis. Animal welfare will also be used as a trade barrier in imports-exports worldwide.

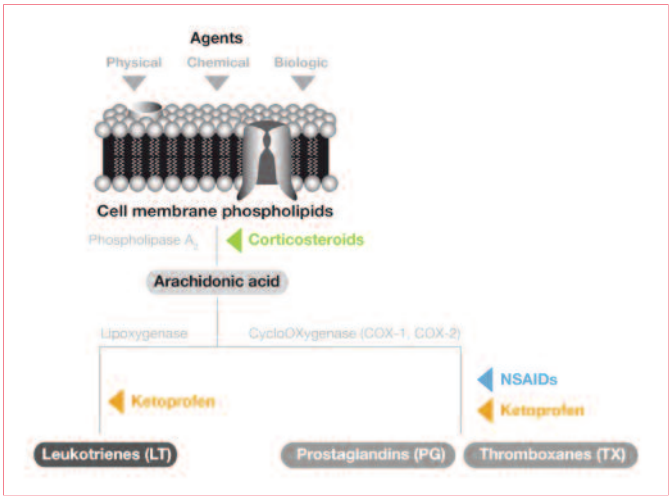

Fig. 2. Site of action of corticosteroids, NSAIDs and ketoprofen. Arachidonic acid is freed from the phospholipids from the cellular membrane by the enzyme phospholipase A2 (PLA2). Corticosteroids act on this enzyme. On the other side, NSAIDs act on cyclooxygenase enzyme, which converts arachidonic acid in prostaglandins and thromboxanes. Some NSAIDs such as ketoprofen also act on lipoxygenase enzyme.

Veterinary clinicians should consider the use of NSAIDs over the use of corticosteroids in current practice to diminish the risk of associated adverse effects, such as suppression of the immune response, more susceptibility to bacterial or viral infections, masking signs of infection, and negative effects on gestation, among others. There are several types of NSAIDs and the veterinary practitioner should get familiarised with its use in order to choose the best for each situation. ■

References are available from the author on request