

Ketoprofen and NSAID use in Cattle

Background

Several different Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are registered in New Zealand and other countries for the treatment of pain, fever and inflammation. Increased NSAID use in cattle in recent years has led to improved animal health and productivity outcomes as well as well-being and sustainability advances.

When considering NSAIDs for use in cattle, products can be grouped into those recommended for administration on a daily basis (eg ketoprofen, flunixin), indeterminate length of action (tolfenamic acid), and longer-acting products (carprofen, meloxicam) where effects last for longer than 24 hours.

Ketoprofen is the most popular NSAID administered to NZ cattle. National sales data shows that over 50% of all NSAID doses administered to NZ cattle contain ketoprofen, i.e. more than meloxicam, carprofen, tolfenamic acid, and flunixin doses combined. There are many reasons for ketoprofen's wide-spread use and popularity, a number of which are outlined below.

Efficacy

Ketoprofen is a highly effective NSAID for cattle. It acts on both cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, dampening down the inflammatory cascade.

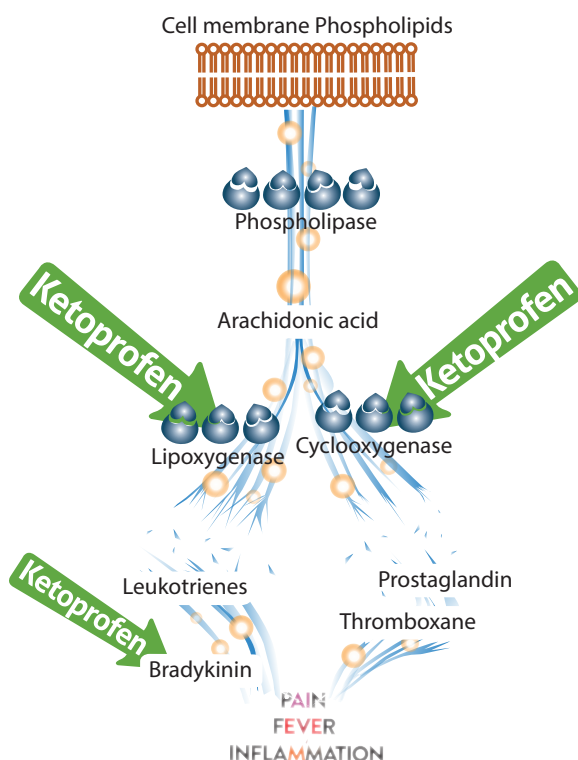


Figure 1. Inflammatory cascade and sites of action of ketoprofen

The model used for testing anti-inflammatory efficacy is to inject lipopolysaccharide (LPS, the substance naturally released by gram negative bacteria, causing inflammation and endotoxaemia) into animals as an infusion. Anti-inflammatory treatment is subsequently provided to the LPS-challenged animal and clinical signs of endotoxaemia are monitored, along with measurement of inflammatory mediators such as plasma thromboxane, prostaglandin F1 α , E2 and leukotriene B4. Inflammatory cytokines such as tumour necrosis factor α , interferon γ , and interleukin may also be measured, depending on the study.

Using this widely accepted artificial model, various studies have shown ketoprofen to be a highly efficacious anti-inflammatory (including endotoxaemia treatment) in cattle^{1,2}.

The Bradykinin Effect

Bradykinin is a protein that is an inflammatory mediator, produced at the site of an injury. Bradykinin binds to specific nociceptors which results in pain in the animal. It also causes hyperalgesia by sensitisation of nociceptors through the production or release of other mediators.

Ketoprofen has been shown to have a direct effect on the bradykinin mediated pain response by blocking binding of bradykinin at the nociceptive receptors. Hence ketoprofen has strong pain relieving qualities via the bradykinin pathway, over and above its anti-inflammatory efficacy.

Considerations for NSAID use in Cattle

NSAID duration of action can be an important factor when treating cattle. On NZ farms authorising vets are generally seeking farmers to re-examine and / or re-treat cattle (with antibiotics) daily in common scenarios when NSAIDs are used. Consequently encouraging greater use of any suitable NSAID is the key to success.

Milk withholding periods can be an important consideration when NSAIDs are administered to dairy cows. Most NSAIDs have nil milk withholding period in cattle. However, meloxicam withholding period is 84 hours following the last treatment. As dairy farmers generally seek to avoid discarding milk for several days if feasible, meloxicam is primarily used as an adjunct treatment along with antibiotics in dairy cows, or in non-lactating animals.

Meat withholding periods for cattle also vary substantially between NSAIDs, from between two days and 28 days depending on the NSAID and data supplied.

The NSAID dose volume for a 500kg dairy cow ranges from 10mL to 30mL. Farmer compliance and dose surety may be improved with a single 10mL dose. Method of application is another factor, with uptake by farm staff often increasing if NSAIDs are provided with an injector gun delivery system.

An important consideration for vet medicines such as NSAIDs is the value perceived by the farmer. The value proposition for farmers using daily NSAIDs, such as ketoprofen, is widely accepted. It allows judgement regarding the need for additional doses on subsequent days depending on the animal's response to treatment (whether pain and/or inflammation remains).

When the NSAID treated animal requires rapid treatment (eg dystocia, down cow) and / or should be re-examined on a daily basis (eg mastitis) then the daily NSAID ketoprofen is generally a good option, as another dose can be administered 24 hours later if required. Conversely, when an animal has surgery and will not be re-examined for several days then a single long acting NSAID dose is more appropriate.

Concerns with Flunixin use in Cattle

The seasonal nature of NZ dairy farming means that cows are required to be successfully rebred in a very short period of time following calving. It is essential that our interventions do not have any likelihood of negatively impacting the cow's chances of becoming pregnant in the months following calving. It is the veterinary professional's motto to "first do no harm". Weight of evidence^{3,4,5,6} is clear that the safest daily NSAID for periparturient use in cattle is ketoprofen. Ketoprofen does not have any negative impacts on incidence of retained foetal membranes (RFM), uterine involution and subsequent reproductive performance.

In contrast several authors concluded that flunixin should not be administered to dairy cattle within 24 hours of parturition. This is because there is evidence that periparturient use of flunixin increases the incidence of RFMs in cows.

Ketoprofen is non-irritant and can safely be administered by the intravenous (IV) or intramuscular (IM) routes. In contrast, another NSAID registered for use in cattle, flunixin has a significant level of tissue irritancy, causing pain and damage at the site of injection⁷. This is likely the reason flunixin is only registered for intravenous use in USA.

As a final consideration, intramuscular administration of flunixin alters the pharmacokinetic properties of the drug (all published pharmacokinetic data is from intravenous use). Intramuscular use of flunixin is of major concern in the USA as this has caused significant milk residue issues⁸.

Summary

Daily NSAID use in NZ dairy cattle is growing rapidly as farmers become more aware of the health, wellbeing and productivity benefits.

Ketoprofen is the most widely used NSAID in NZ cattle. An effective anti-inflammatory and a powerful anti-endotoxaemic drug, ketoprofen controls pain by its direct effect on bradykinin mediated pain. Ketoprofen is safe to use in periparturient cows, having no effect on RFM's or subsequent reproductive performance. It does not cause pain or tissue damage after intramuscular administration.

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