The use of meloxicam (Metacam 20®) in bovine practice in South Africa

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Introduction
Meloxicam is an acidic non-steroidal anti-inflammatory drug (NSAID) used in human as well as veterinary medicine. Like all other NSAIDs, it has a non-steroidal structure, and acts on the arachidonic acid cascade in the inflammatory process by inhibiting the production of Prostaglandin H₂ through the enzyme cyclo-oxygenase (COX). Different isoforms of COX exist, which leads to the formation of different end-products in the cascade. Occupation of the COX-1 receptor is responsible for the decreased production of prostacycline (PGI₂) which plays an important role in renal and gastro-intestinal tract integrity. On the other hand, the COX-2 form controls the formation of thromboxane (TXA), affecting platelet function, as well as prostaglandin F₂α (PGF₂α) and prostaglandin E (PGE), both important inflammatory mediators. Most of the older NSAIDs do not bind to COX receptors selectively, and for that reason, while having anti-inflammatory effects through the prevention of the formation of PGF₂α and PGE, also inhibit the formation of PGI₂. This inhibition of PGI₂ is the cause of the most important side effects of NSAIDs, namely gastro-intestinal ulceration and renal toxicity. The toxic effects occur in particular in the presence of poor blood circulation in the intestinal mucosa and kidneys, which can be due to dehydration, septicaemia or other forms of shock, and is often the case in sick animals. The presence of other substances with intestinal or renal toxicity may exacerbate the toxic effects of (particularly non COX-selective) NSAIDs. Meloxicam has a COX-2 preferential action, although some COX-1 effects can occur at increased dosages.

In bovines, meloxicam has good bio-availability, which are very similar after different routes of application including the oral route, and has a plasma half-life of +/- 27 hours (range: 20-43 hours). Meloxicam is 98% plasma-bound in cattle, and is metabolised in the liver and to a lesser degree in the kidney. Metabolites are not pharmacologically active, and excretion of metabolites occurs through faeces (via bile) and urine. Like most other NSAIDs, some of the parent molecule of meloxicam is excreted through milk, which leads to a decrease in plasma half-life to 17 hours in lactating cows.

Despite its availability in several countries for use in cattle practice for more than a decade already, meloxicam (Metacam 20®) only became available to the South African cattle practitioner in June 2012, while many other countries including the USA have not yet allowed registration of the drug in food-producing animals, despite very extensive studies on the safety and efficacy of the drug. The timing of the release of meloxicam in the South African market was very good due to concerns about the safety of, and re-classification of some alternative NSAIDs.
The 20mg/ml formulation of meloxicam is registered in South Africa with a 5-day milk and 15-day meat withdrawal in cattle. The registered dose for cattle is 0.5mg/kg by subcutaneous or intravenous injection. It is also registered for use in pigs and horses.

Toxicity studies of meloxicam in rats indicated mostly intestinal tract disturbances (diarrhoea), reduction in haemoglobin concentration and haematocrit, and increase in hepatic enzymes indicating liver toxicity.

**Indications for Meloxicam in bovine practice**

**Analgesia**
Meloxicam has been demonstrated to have good analgesic effects in cattle. In an experiment using meloxicam combined with a cornual nerve block prior to dehorning, meloxicam reduced post operative pain for up to 44 hours. Meloxicam has also been shown to prevent the relapse of pain after the effect of a corneal block has worn off in dehorned calves. In another study meloxicam reduced pain and improved feed intake, feed conversion and growth rate in feedlot calves after castration. Meloxicam has also been shown to reduce pain responses associated with clinical mastitis, and the practical application in this study indicated that analgesic response to one single meloxicam treatment at the first occurrence of clinical signs did not differ significantly from the response after repeated treatment.

Meloxicam has a preferential accumulation in inflammed synovial joint fluid in dogs and rats, and this may explain its superior analgesic effect in musculo-skeletal disorders. This is thought to be because of increased permeability of blood vessels supplying inflamed sites allowing protein-bound meloxicam to exit blood vessels, as well as due to the increase in pH of the inflamed area, causing the drug to be less plasma bound at these sites. If this applies to other species as well, together with the long duration of analgesic action in bovine patients, the use in cases suffering from bovine ephemeral fever (three days stiffness) appears promising.

The effects of pain management on production performance is a current topic of research, and in a recent publication on the effects of meloxicam treatment on production performance after castration, a temporary improvement (up to day 14) in production (average daily gain, feed conversion ratio) was shown. This was however mitigated by compensatory growth until day 28 in untreated control animals. An increase in dry matter intake, and a reduction in incidence of respiratory disease was however demonstrated up to day 28 in calves receiving meloxicam before castration.

Due to consumer demands as well as the social standing of the veterinary profession, welfare of production animals is likely to become more important in future veterinary practice.

**Anti-inflammatory, anti-endotoxic and anti-pyretic effects**
Anti-endotoxic effects of meloxicam were shown in calves given endotoxins to induce clinical illness. Meloxicam reduced the increase in Thromboxane and clinical signs associated with endotoxaemia 50 hours after administration.
In a more detailed study in heifers, meloxicam was shown to have strong anti-endotoxic and anti-inflammatory effects, including a prevention of the release of prostaglandin and a reduction in cortisol release, as well as less severe depletion in serum Fe, Zn and Ca. In this trial meloxicam did not prevent the pyrogenic effect of endotoxin. Although this was mentioned in some other trials as well, it is not a consistent finding.

From another study it seems that the anti-inflammatory effects of meloxicam are limited to eicosanoids that act as pro-inflammatory mediators, including thromboxane, prostaglandins and malonyldialdehyde (MDA), while activating early immune mediators such as leukotrienes which are responsible for the stimulation of neutrophil function, through the lipoxygenase pathway.

A superior suppression of prostaglandin was reported for meloxicam when compared to flunixin and ketoprofen, in a study that determined the most appropriate NSAID to be used in a treatment protocol for repeat breeder dairy cows, and an attempt to prevent premature luteolysis. Meloxicam treatment in this study increased the inter-oestrus interval by 1 day when given on day 17 of the oestrus cycle.

**Bovine Respiratory Disease (BRD)**

Several studies have emphasised the beneficial effect of NSAIDs, including meloxicam, in the treatment of BRD. BRD is an economically very important disease, in particular in the beef feedlot industry, and an important component in the pathogenesis of the disease complex is the vicious cycle caused by chemotaxis and the resultant release of lysosomal products from neutrophils. Other inflammatory mediators add to the inflammatory process by causing circulatory changes in the lungs, as well as fibrinisation of the lung and pleural surfaces.

In a controlled study performed on young calves (+/-100kg starting mass) with BRD in Europe, significant increases in weight gain and carcass mass, and a significant decrease in lung scores were observed in calves treated with meloxicam in conjunction with antibiotic treatment, compared to those treated with antibiotics alone. In a similar study meloxicam added to an antibiotic treatment of BRD led to a reduction in production losses associated with BRD (growth rate) when compared to flunixin and negative control animals.

In another study that compared immunological responses in broncho-alveolar leukocytes in young calves (+/-75kg) with bronchopneumonia treated with either flumethasone or meloxicam, it was suggested that meloxicam was a more appropriate anti-inflammatory choice in these cases, due to the fact that the steroidal anti-inflammatory suppressed non-specific immunity through decreased neutrophil and lymphocyte numbers while this response was not seen in meloxicam treated calves.

Unfortunately no trials have been reported on the effects of meloxicam in feedlot cattle under South African conditions. Although extrapolation is probably in order, calves under local conditions are challenged by different pathogens, and are exposed to different environmental effects, which may have an effect on the performance of a particular NSAID treatment. However, one reported trial in a feedlot in Mexico (mean calf mass 220kg) simulates the South African conditions more closely than European studies performed on very young calves. In this trial meloxicam was compared to flunixin meglumine as supportive treatment of BRD. Unfortunately there was no negative control group in the trial, and the only differences reported were a lower mean rectal temperature 2 days after the onset of treatment in the meloxicam group, and a higher treatment frequency in the flunixin group.
The difference in treatment frequency was however due to label instructions of the two drugs. No difference in production performance was reported.

**Diarrhoea in calves**
Meloxicam has been shown to have anti-inflammatory, analgesic, as well as anti-secretory effects in calves with diarrhoea, regardless of the underlying cause. In some forms of diarrhoea, prostaglandins may also have a spasmodic effect on the gastro-intestinal tract, which is alleviated by the use of an NSAID. However, due to the potential ulcerogenic effect of NSAIDs, in particular in patients with reduced blood circulation through the intestinal wall, only NSAIDs that are COX-2 preferential or selective can be used safely in cases of calf diarrhoea.

In a controlled study of undifferentiated calf diarrhoea, meloxicam treatment resulted in increased feed and water intake and increased growth rate after treatment when compared to control calves. This led to earlier weaning from milk in the treated calves. Although no studies have been performed under South African conditions, the aetiologies of calf diarrhoea are reasonably cosmopolitan, and results from other locations are probably applicable to local conditions.

**Acute mastitis**
Somewhat similar to the pathogenesis of BRD, the inflammatory process also plays an important role in the course of acute mastitis in dairy cows. Initial bacterial colonisation due to the failure of physical barriers leads to the release of cytokines from macrophages and epithelial cells, which attract the polymorphonuclear neutrophils. These cells are the primary phagocytes, but the mechanism is only effective when bacteria can be overcome rapidly. If this does not happen, bacterial toxins and inflammatory mediators from neutrophils cause more damage to mammary tissue. Depending on the bacteria involved, the following acute mastitis can vary a lot in pathological and clinical course, from those associated with very severe endotoxaemia that may lead to mortality, to those that will lead to micro-abscessation in the mammary parenchyma.

In a large study on the effects of treatment on the outcome of (mild) acute clinical mastitis in Nieu-Zeeland, inclusion of meloxicam in the treatment protocol led to a significant decrease in post-treatment somatic cell count (SCC) in affected cows, as well as a significant reduction in culling rate after treatment. No effect was demonstrated on production performance or re-treatment rate of cows treated with meloxicam.

Treatment for mastitis is a label indication for Metacam 20® in South Africa. The recommendation is to give one treatment at the onset of clinical signs. Although the results of this study may be applicable to South African conditions, it has to be kept in mind that the bacterial spectrum seen in mastitis in South African dairies differs from that seen in the Nieu-Zeeland study, and clinical response may vary dramatically depending on the underlying bacterial cause. Antibiotic treatment route may also be an important factor to consider, as in the reported study all cows were treated with a systemic antibiotic only.

**Abomasal and intestinal ulceration in cattle**
Smaller ulcers occur commonly in the intestinal tract of particularly high producing cattle, and will surely affect the production potential of the animal. However, it only leads to clinical signs when a
blood vessel is penetrated, or when the ulcer perforates through the full thickness of the abomasal wall to cause peritonitis.

A type of “homeostasis” exists across the abomasal mucosa between the insult, namely chemical or physical damage on the one hand, and the protective mechanism, namely the mucous and bicarbonate layer and tight junctions between the epithelial cells on the other hand. An increase in the insult leads to increased production of prostaglandins I and E, which in turn leads to a decrease in acid production, stimulation of the formation of the protective layer (mucin and bicarbonate) and increased blood flow to the submucosa. This “homeostasis” can be disturbed by various factors that have effects on the protective layer, or on the production of hydrochloric acid. Further, a balance also exists between the formation, and healing of ulcers under normal circumstances, and if this balance is disturbed, the ulcer will get bigger and can start to bleed or perforate.

Several factors play a role in the formation or persistence of ulcers, including the diet, diseases, stress and the use of NSAIDs. NSAIDs accelerate the process of ulcer formation and impair the normal healing process. Some controversy still exists about the exact relationship between COX selectiveness and ulcerogenicity, for instance is ibuprofen quite ulcerogenic despite it being COX-2 selective, and it seems that inhibition of COX-2 may cause impaired healing of small intestinal ulcers. Of the NSAIDs commonly used in bovine practice, phenylbutasone is the most ulcerogenic, while flunixin is intermediary.

**Non-steroidal anti-inflammatory drugs and nature conservation**

Since the discovery of the toxic effects of NSAIDs (in particular diclofenac) to *Gyps* vultures that caused the Oriental vulture to be at a high risk of extinction, a lot of research was done on the safety of NSAIDs in different bird species, in particular scavenger species that may be affected by the consumption of carcasses from animals that died after treatment with NSAIDs. This is particularly relevant in South Africa with its large number of vulture restaurants, and also for practitioners wanting to use NSAIDs in wildlife species.

According to a survey performed in 2006, toxicity has been observed in birds after exposure to a number of different NSAIDs. Meloxicam and ketoprofen, however, have not been implicated in any cases of toxicity to birds. In a separate study however, toxicity by ketoprofen was shown in vultures, leaving meloxicam as the only safe NSAIDs for use in scavenging birds. The safety of meloxicam has been tested in separate studies Cape Griffons and white-back vultures, as well as in a range of Indian vultures and other scavenging birds, and was tolerable at dosages up to 2mg/kg for extended periods of time. Meloxicam has a short half-life in vultures.

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