Meloxicam

– A literature review –

2016*

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* The original review was written in October 2009.
In February 2015 the chapters 2.1.4, 2.3.1 and 2.3.2 have been added.
The document has been revised in 2016.

Content

1. Introduction

In July 2009 Dopharma Research registered Melovem® 5 mg/ml, the first generic meloxicam injection for cattle and pigs. This product is registered via the centralised procedure in all European Union member states plus Iceland, Liechtenstein and Norway. In September 2013, the range was extended with Melovem® 20 mg/ml and 30 mg/ml. Melovem® 20 mg/ml is also registered for use in horses.

The active ingredient of Melovem® is meloxicam. To extend our knowledge of this molecule, we extensively studied the available scientific literature, which resulted in this literature review.

1.1 History of meloxicam

1.1.1 The use of NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used by humans in various forms for over 3 500 years. Their popularity is still enormous; it is estimated that humans around the world consume around 50 000 metric tons of aspirin each year, equating to about 80 tablets per person per year.

1.1.2 Their mechanism of action and selectivity

Despite this long history and the large volumes used, the mechanisms of how NSAIDs achieve their actions are still not completely unravelled [1].
Some 30 years ago, it was first revealed that these drugs all reduced the formation of prostaglandins and that this ability was associated with inhibition of the enzyme cyclooxygenase (COX). COX converts arachidonic acid to the prostaglandin precursor prostaglandin H_2 (PGH_2). In the early 1990s the existence of two isoforms of COX, COX-1 and COX-2, was discovered, leading to the categorisation of all NSAIDs according to their specificity to each of these isoforms [2].

Meloxicam is an NSAID of the oxicam class that acts by inhibiting the prostaglandin synthesis and inducible COX-2, thereby exerting anti-inflammatory, anti-exudative, analgesic and antipyretic effects [3-5]. The molecule is highly plasma protein bound when circulating in the body: 95-99%. It has a long plasma half-life, enabling less frequent dosage schemes.

Recently, its marked anti-endotoxic activity has been shown; meloxicam inhibits the production of thromboxane B_2, induced by intravenous E. coli endotoxin to calves and pigs and the intra-mammary administration of E. coli endotoxin to lactating cows [6].

1.2 Mechanism of action and potential adverse events

Stimuli of various origin, such as infectious agents, trauma, and neoplasia, can trigger the cascade of processes involved in inflammation. An important step in this process is

the conversion of arachidonic acid into the prostaglandin precursor PGH_2 by the enzyme cyclooxygenase (COX).

1.2.1 COX-1 and COX-2

COX-1, a constitutive enzyme, supports the production of physiologically relevant prostaglandins regulating the production of cytoprotective gastric mucus and controlling renal blood flow and platelet aggregation. Inhibition of COX-1 is responsible for the known potential adverse events of especially older NSAIDs. The most important adverse events are ulceration of the upper gastrointestinal tract and delayed blood clotting.

COX-2, an inducible enzyme, is responsible for the formation of pro-inflammatory prostanoids; these prostanoids are for a large part responsible for the undesirable effects of the inflammatory reaction, such as pain and fever.

1.2.2 COX-2 selective drugs

COX-2 selective drugs have the same anti-inflammatory potential as the traditional NSAIDs but with reduced adverse events, particularly on the gastrointestinal tract [1, 7]. In inflammatory models COX-2 inhibitors were indeed as active as traditional NSAIDs, but the widespread use of the newer generation of COX-2 selective compounds demonstrated that COX-2 also had physiological roles, being involved for instance, in the maintenance of the fluid balance by the kidney [8].

The COX-1/-2 model could not explain everything. The model is for instance certainly not accommodating for the characteristics of acetaminophen (paracetamol). Its antipyretic and analgesic effects might be explained by inhibition of COX-2, but why does acetaminophen not have any anti-inflammatory effects [9]?

1.2.3 Meloxicam

In comparison with various other human NSAIDs, meloxicam proved to be a potent inhibitor of oxyradical production at drug concentrations comparable with those encountered during therapy [10].
Systemic meloxicam produces analgesia largely via peripheral mechanisms. The rapidity of its actions indicates a direct effect on sensitised nociceptors.

Meloxicam has been studied in horses by Kamerling et al. A dose of 0.6 mg/kg was administered to ponies, and responses to carrageenan-induced acute inflammation were recorded. Meloxicam reduced heat, protein, lactic dehydrogenase, leukocyte numbers, PGE_2, and thromboxane B_2 in exudates obtained from the site of inflammation. This effect was greatest at four to eight hours. Meloxicam levels gradually increased over time at the inflamed site [11].

The pharmacokinetics and pharmacodynamics of meloxicam in piglets of 16-23 days old were studied by Fosse et al. The results indicate an inadequate inhibition of inflammation in piglets (0.4 mg/kg BW). The most marked inhibition of PGE_2 was measured at four hours; the mean concentration in the meloxicam group being 46% lower than in the placebo group [12]. This could be insufficient, as other studies have demonstrated that

the PGE_2 synthesis at the site of inflammation needs to be inhibited by 80% or more to achieve a clinically relevant antipyretic, anti-inflammatory or analgesic response [13, 14]. In piglets, behavioural and physiological pain scores have demonstrated the analgesic effect of meloxicam on post-operative pain, using a much higher dose, but also a different method of administration (1 mg/kg intra-arterial) than the marketed dose for adult pigs (0,4 mg/kg) [15].

1.3 Specific safety issues

Meloxicam is a COX-2 preferential NSAID. This is explained in more detail in the paragraph about the mechanism of action. Meloxicam however also inhibits the COX-1 iso-enzyme. The cardiovascular effects of selective COX-2 inhibitors include myocardial infarction and cerebral vascular events. These adverse events observed in human medicine occur at therapeutic doses after long-term use only.

The available pharmacovigilance data for Melovem® have not demonstrated any particular cardiovascular effects or thrombotic events associated with the substance [16]. Specific adverse events related to the inhibition of COX-1, such as gastric and duodenal ulceration and coagulation disorders, are rare. They however might occur, especially with high and/or prolonged dosages.

In cattle and pigs, subcutaneous, intramuscular as well as intravenous administration is well tolerated; only a slight temporary swelling at the injection site following subcutaneous administration was observed in less than ten percent of the cattle treated in clinical studies [17]. Friton et al. also did not notice any adverse events in a field study with meloxicam in pigs [3].

In horses, anaphylactic hypersensitivity reactions can occur and should be treated symptomatically. A temporary swelling at the injection site can occur but resolves without intervention [13].

1.3.1 The immune system

Meloxicam appears to have no effect on serum concentrations of acute phase proteins CRP and haptoglobin, which are considered to be important markers of the innate immune system of pigs. Serum concentrations of IgG or IgM antibodies to E. coli endotoxin (LPS) were similar in treated and non-treated pigs. Treatment with meloxicam thus appeared to have no adverse effects on the naturally available level of antibodies to E. coli LPS. Meloxicam does not have an adverse effect on the production of specific IgG and IgM under certain circumstances, and it may therefore be expected to have no adverse effect on vaccination regimes [18].

1.3.2 Pregnancy and lactation

Meloxicam crosses the placenta of pregnant rats and can be detected in foetal tissues at levels similar to those found in the placenta. Both levels remained below plasma drug levels. Meloxicam and/or metabolites were excreted in rat milk, with levels in milk increasing relative to those in plasma over 1 to 24 hours after dosing. Reproductive

toxicity studies in which prolonged and/or high doses of meloxicam were used in Sprague Dawley rats, revealed increases in resorption rates, prolonged pregnancy and decreased pup viability [19].

Friton et al. injected pregnant sows with meloxicam at a dose rate of 0.4 mg/kg. They administered a single injection, followed by a second injection if needed. Meloxicam proved safe to use in pregnant sows [3].

1.4 Pharmacokinetics

After intramuscular or subcutaneous administration, meloxicam is usually well absorbed. Species differences do occur. In many species, the volume of distribution is low for most NSAIDs [14]. This is probably caused by the extreme binding to plasma proteins. Meloxicam is no exception to this phenomenon [12, 20].

The proposed metabolic pathway of meloxicam in pigs is hepatic oxidation to its 5-hydroxymethyl and 5-carboxyl metabolites [20].

Pharmacokinetics in neonatal animals can be different from adults. The metabolic pathways of hepatic oxidative reactions and glucuronide conjugation can be deficient in piglets for up to six weeks of age [21]. Such differences can usually be attributed to altered disposition processes during the neonatal period, which again can affect the plasma concentrations as well as the concentrations of drug attained at the receptor sites.

Substantial concentrations of meloxicam are attained in synovial fluid, the proposed site of action in chronic inflammatory arthropathies [22].

2. Species specific applications

2.1 Cattle

2.1.1 Respiratory disease

Bovine respiratory disease complex (BRD) is a major problem in the feedlot industry causing significant economic losses and threatening animal welfare. It is a multi-factorial disease, caused by the interaction of factors like stress, reduced immunity, and respiratory pathogens. Following virus- and/or stress-induced impairment of the animal's respiratory defence mechanisms, bacteria such as Mannheimia haemolytica or Pasteurella multocida can invade the lower respiratory tract, resulting in a clinical outbreak.

In cattle surviving the acute phase of fibrous pleuropneumonia, the associated lung lesions rarely resolve completely. Such lesions are associated with decreased productivity, such as decreased daily live weight gain, reduced general performance and poorer carcass quality [23-25]. A major factor in the pathogenesis of severe lung damage appears to be the excessive inflammatory response [25]. Bednarek et al. showed that the addition of an NSAID (meloxicam or flunixin meglumine) to the treatment with oxytetracycline had significant positive effects on the production of the tumour necrosis factor (TNF). Excessive general TNF production, resulting in high cytokine serum levels, was inhibited. BAL[1]-cells were however still able to produce TNF, in contrast to those of the control group.

Addition of meloxicam to an antimicrobial therapy does not exert an immunosuppressive effect in calves suffering from enzootic bronchopneumonia and results in a therapy superior to that of antimicrobial therapy alone [26]. Decreasing the inflammatory response in the early stages of the disease by using meloxicam will aid to reduce the severity of the lesions and improve the animals' performance in comparison with animals receiving antibacterial therapy alone [27]. Combined therapy of oxytetracycline with meloxicam induced a stronger reduction of clinical signs and faster normalisation of the rectal temperature. It also had beneficial effects on functional parameters of the respiratory system [26].

Long-term evaluation of the addition of a single subcutaneous injection of meloxicam to an antimicrobial treatment (oxytetracycline or florfenicol) revealed a significantly better performance, with higher mean live weights and carcass weights [27, 28].

A single subcutaneous dose of meloxicam (0.5 mg/kg BW) is as clinically effective as up to three consecutive daily intravenous doses of flunixin meglumine when used as an adjunctive therapy to antibacterial therapy in the treatment of acute febrile respiratory disease in feedlot cattle [29].

[1] BAL: Bronchoalveolair lavage: Via a flexible tube, inserted through the nose, sterile isotonic saline is instilled into a bronchus in a volume large enough to reach the connected alveoli; the saline is then retrieved for analysis.

Often, the respiratory tract is primarily infected by viruses, enabling bacteria to cause secondary infections. In human medicine, treatment of such primary viral respiratory infections is usually supportive; doctors send you home with the advice to 'take it easy' for a few days under prescription of NSAIDs. Merck Online Medical Library states: "Antibacterial drugs are ineffective against viral pathogens, and prophylaxis against secondary bacterial infections is not recommended. Antibiotics should be given only when secondary bacterial infections develop. In patients with chronic lung disease, antibiotics may be given with less restriction" [30].

Veal calves nowadays are usually kept on large farms and in groups, which makes it difficult to notice the first calves with upper respiratory symptoms. On many farms, the veterinarian will not be called until a certain amount of animals have already moved on to the secondary phase with bacterial involvement and spread of the disease into the deeper airways. Very accurate farmers are sometimes able to successfully treat a primary viral infection by swift and accurate use of NSAIDs plus some TLC (Tender loving care). In many of these animals antimicrobial therapy can be avoided or delayed. The latter is concluded from experiences of Dutch veal calf specialists in the Netherlands.

2.1.2 Diarrhoea

Diarrhoea in calves is a clinically and economically important disease; the incidence ranges from 10 to 35% and it is estimated that diarrhoea accounts for more than 50% of pre-weaned calf deaths [31].
The major causes of diarrhoea in the first three weeks of life are:

- Bacterial
    - Enterotoxigenic Escherichia coli
    - Salmonella enterica subspecies enterica serovars
    - Clostridium spp Type C
- Viral
    - Rotavirus
    - Coronavirus
    - Bovine viral diarrhoea (BVD)
- Parasitic
    - Coccidiosis
    - Cryptosporidium parvum type II
- Non-infectious
- Nutritional issues

Calves may be infected with a diverse array of Salmonella serotypes within hours of birth [32]. Diarrhoea is often complicated by signs of systemic disease, such as fever, inappetence and lethargy.
Regardless of aetiology, calves with diarrhoea often have increased coliform bacterial numbers in the small intestines; small intestinal bacterial overgrowth is associated with an altered function [32, 33].

Bacteraemia is a common feature of salmonellosis in calves, requiring aggressive treatment with antimicrobials early in the course of infection. In human medicine, however, invasive salmonella infections are uncommon and routine use of antimicrobial therapy is not recommended. This has led to some controversy surrounding the use of antimicrobials to treat salmonellosis in livestock. There are concerns about the selection for antimicrobial resistance and questions regarding the necessity and efficacy, which are largely derived from experience in human medicine [32].

Todd et al. conclude that a single injection of meloxicam at the onset of diarrhoea is an effective supportive therapy for calves in terms of calf performance, appetite and animal welfare. The treatment improved milk consumption during an episode of neonatal calf diarrhoea complex, as well as increased intake of starter ration and water [31].
Treating calves suffering from diarrhoea with meloxicam clinically results in a decreased body temperature, an increased faecal consistency, increased milk and feed intake and an increased bodyweight. Additionally these calves could be weaned earlier and required less additional antibiotic therapy [34].

Results of several studies suggest that meloxicam should be considered as part of the initial treatment of calves with diarrhoea and systemic illness [35, 36]. Use of meloxicam (0.5 mg/kg BW) has been reported to improve the outcome and reduce the morbidity in calves with non-specific diarrhoea [36]. An empiric guideline for the treatment of diarrhoea is to administer meloxicam or flunixin meglumine preferably once, but never more than three times. This recommendation is based on the need to avoid damaging the abomasal mucosa, particularly in intensive calf-rearing facilities with a history of calf deaths due to perforated abomasal ulcers [33].

2.1.3 Dehorning

Hot-iron dehorning is a routine husbandry practice performed on calves, typically between two to six weeks of age, which prevents horn development by removing the horn buds using heat cauterisation. This should be done at an early age, because after the horn bud develops and becomes fixed to the skull, amputation dehorning is necessary [37]. This is considered more painful than hot-iron dehorning [38]. The purpose of dehorning is to minimize the risk of injuries to the animal itself, and also to stockpersons and other animals.

Several studies have shown that, when no local anaesthetic is used, pain associated with hot-iron dehorning lasts for at least two to three hours [39, 40]. Dehorning is associated with an elevated serum cortisol and heart rate, in some cases even when a direct corneal nerve block with a local anaesthetic was performed [41]. Other studies showed that lidocaine can essentially eliminate the cortisol response to dehorning, when a ring block is used [40, 42].
Use of local anaesthesia can reduce behaviour indicative of the acute pain. Lidocaine, most commonly used for dehorning, is only fully effective for approximately two hours after administration, after which pain-related behaviour, cortisol concentrations, and inflammation-related pain increase [38]. In the third hour after hot-iron dehorning in

calves that had received local anaesthesia, increased head shaking was observed [39], as well as an increase in the heart rate, even when cortisol concentrations had declined after one hour. This suggests that cortisol responses to dehorning may be a consequence of the immediate noxious stimulus rather than representing the ongoing pain experienced [43].

Observations of pain-related behaviour at three and 24 hours after hot-iron dehorning demonstrated that pain continues well beyond the established peaks in cortisol. The addition of an NSAID (ketoprofen), beside xylazine sedation and local anaesthesia, reduced ear flicking for up to 24 hours, and head shaking for up to twelve hours [44]. The use of meloxicam, beside local anaesthesia, decreases the cortisol levels after 30 minutes and respiratory rates permanently returned to base-line levels after two hours. Cortisol may better represent stress of handling or general discomfort, whereas heart rate and respiratory rate are better indicators of post-surgical pain. When compared with controls, calves that received meloxicam had lower heart and respiratory rates after dehorning, as well as lower cortisol concentrations during six hours after dehorning. Meloxicam-treated calves even showed significantly lower serum cortisol than control calves immediately after dehorning. It can be concluded that meloxicam (0.5 mg/kg BW), given ten minutes prior to dehorning, reduces the stress response caused by dehorning surgery [41].

Studies investigating the pain associated with amputation dehorning have shown that a combination of local anaesthesia and an NSAID was required to alleviate both the acute pain and the longer term pain [38, 43].

When NSAIDs with a shorter duration of action are used, cortisol levels will rise again after some hours. This was demonstrated by studies using ketoprofen; little or no additional beneficial effect was seen to the use of lidocaine alone and there was a second cortisol peak at five to six hours after dehorning [42, 45]. The half-life of flunixin meglumine is also shorter than that of meloxicam [46]. Repeat doses of such drugs are required for adequate postsurgical analgesia.

2.1.4 Mastitis

Mastitis is defined as inflammation of the mammary gland and is often associated with infection. Etiologic agents are commonly divided into those causing contagious mastitis, opportunistic mastitis and environmental mastitis. Pathogens are further divided into major pathogens and minor pathogens. Major pathogens are usually those that cause clinical mastitis while minor pathogen cause subclinical mastitis in the majority of cases [47].

Mastitis is still a prevalent and economically detrimental disease in the dairy industry. Mastitis results in economic loss for producers by increased production cost and decreased productivity. The premature culling of potentially profitable cows is also a significant loss [47]. The negative effects of clinical mastitis regarding discomfort, pain, and reduced welfare are well known but probably underestimated. A large portion of mastitis cases concern subclinical cases.

The pathogenesis of mastitis can be explained in terms of three stages: invasion, infection and inflammation. Invasion is the stage at which pathogens move from the teat end to the milk inside the teat canal. Infection is the stage in which the pathogens multiply rapidly and invade the mammary tissue. Multiplication of certain organisms may result in the release of endotoxins which causes profound systemic effects with minimal inflammatory effects. Inflammation follows infection and represents the variable systemic effects and the stage of clinical abnormalities of the udder such as swelling, heat and oedema.

Intramammary infection generally triggers an immune response resulting in an elevated somatic cell count (SCC); cytokines, prostaglandins and complement system attract white blood cells into the mammary gland [48, 49]. Neutrophils are the predominant cells. Arrived at the site of infection they phagocytise and kill pathogens. Neutrophils exert their bactericidal effect through a respiratory burst that produces hydroxyl and oxygen radicals which are components of the oxygen-dependent killing mechanism. The severity and duration of mastitis are related to the promptness of the neutrophil migratory response and their bactericidal activity at the site of infection [47].

Currently optimized treatment strategies focus on efficacy, economics, animal welfare aspects and the milk withdrawal time. Several studies show beneficial effects of meloxicam in the treatment of mastitis. Fitzpatrick et al. concluded that meloxicam can help to mitigate the signs of pain, discomfort and stress that are associated with mastitis [50]. Milne et al. concluded that promoting recovery of moderate or mild mastitis by alleviating pain will improve cattle welfare [51]. Other studies in which lactating dairy cows have been treated with meloxicam have reported the alleviation of pain and discomfort associated with mastitis, by reducing heart and respiratory rates and pain responses [6]. In addition, meloxicam has been shown to be an effective pain management therapy as a single intravenous dose administration in conjunction with antibiotics [52].

In another study it was concluded that treating cows with a combination of meloxicam and penethamate resulted in a lower SCC and a reduced risk of culling as compared with the penethamate treatment alone [53].

Oedema scores provide a visual indication of pain due to clinical mastitis. Fitzpatrick et al. showed that cows that were given meloxicam appeared to have a lower, and therefore better oedema score than their placebo counterparts [50]. This is similar to another challenge study, which observed the use of meloxicam with acute cases of clinical mastitis [52]. In their study, the severity of inflammation in affected animals was decreased two days following the identification of a case of mastitis with the use of meloxicam. This differs from a previous study, which looked at the effects of meloxicam on naturally-occurring cases of mastitis, where there was no treatment effect on oedema score [53].

In a recent study it was discovered that meloxicam can also increase the bacteriological cure rate of mastitis and decrease the number of new infections. There are also beneficial effects on fertility. The use of meloxicam resulted in a higher proportion of cows

conceiving to their first artificial insemination, higher pregnancy rates at day 12- post calving and a decrease in the number of artificial inseminations needed to achieve conception [54].

2.2 Pigs

2.2.1 Castration

Castration of piglets is performed routinely in many countries to avoid boar-tainted meat. The procedure induces acute pain in piglets and studies have indicated that piglets may suffer pain for a prolonged period after the procedure [55, 56]. The pain can cause delayed recovery, reduced feed and water intake, reduced immune capacity and impaired welfare [56].

Nowadays, societal resistance towards this procedure is increasing. In Norway, under the current Norwegian Animal Welfare Act, castration must be performed by a qualified veterinarian using anaesthesia, and when castration of piglets older than seven days is performed, it is mandatory to administer a long-acting analgesic. Similar rules apply for castration of piglets older than seven days in the European Union [57]. In Denmark, auditing schemes supervise that pain-relieving drugs such as meloxicam or flunixine meglumine are administered just before castration.
The only long-acting analgesics with a maximum residue limit (MRL) established for use in pigs belong to the class of NSAIDs [12].

Hansson et al. showed that piglets treated with meloxicam (1 mg meloxicam) immediately after castration displayed not only less pain-related behaviour than control piglets on the day of castration, but also on the following day. Based on these results, these authors advice the use of a local anaesthetic in combination with meloxicam [56].

Cortisol concentrations are significantly raised by procedures inducing pain and distress, like castration. Elevated cortisol levels can persist for many hours after the surgery. This stress reaction is not activated by handling or blood-sampling [58]. Pre-operative administration of meloxicam reduces the neuro-endocrine stress reaction induced by castration significantly [59, 60].

Post-operative behaviour is scored as castration-induced signs of pain, activity at the mammary glands and playing. This behaviour is positively influenced by the pre-operative use of meloxicam or flunixin, indicating that these drugs are capable of reducing castration-induced pain in piglets. NSAIDs have no influence on the wound healing processes [59].

Piglets castrated at four to six days old under local anaesthesia with procaine hydrochloride showed a tendency towards a high mean level of cortisol one hour after castration. An intramuscular injection of meloxicam (2 mg/kg BW), 15 minutes prior to castration, prevented any significant increase of cortisol levels during the 28 hours of the experiment [58].

Compared to castration without anaesthesia, the use of the local anaesthetic lidocaine reduces the direct vocal expression of pain during castration, as well as the increase in cortisol. Meloxicam as sole treatment has a limited beneficial effect regarding vocal expressions and no positive effect on physiological parameters like cortisol. The use of lidocaine alone, however, did not have a positive effect on pain-related behaviour after castration; lidocaine-treated pigs showed significantly more specifically pain-related behaviour than piglets in other groups. Lidocaine has a very limited time of action and its 'wearing off' might have caused a sensation that increases tail wagging behaviour [61].

The use of isoflurane inhalation anaesthesia during castration prevents stress during castration, but it will not reduce pain that occurs after the surgery. Meloxicam administration (0.4 mg/kg BW) 15 minutes before castration did however significantly decrease the plasma cortisol levels, from which it can be concluded that the piglets suffered less pain [62].

It can be concluded that beside the use of local anaesthesia, post-operative analgesia is indicated. One injection of meloxicam just before the castration procedure provides a simple and effective means to reduce post-operative pain and stress, enabling swift recovery and normalisation of nursing patterns.

2.2.2 Post-farrowing pain and piglet performance

The pain caused by farrowing may substantially modify the normal behaviour of sows during and after parturition. Abnormal behaviour negatively affects production performance of the sow and piglets [63]. An active sow will have a higher water intake and consequently produce more milk, enabling a higher daily weight gain and lower piglet mortality in the first week [63-65].
A difficult parturition causes extra pain and stress in the sow and her piglets; mortality will increase and it will have negative effects on health and animal welfare in the long-run, for example on group integration, weaning, diseases and fertility. Pain and stress are known causative factors in reduced milk production and mastitis [66].

Studies have shown that meloxicam has an important effect on the behaviour of sows; their activity on the first few days post-farrowing increases when compared with non-treated sows. This is most likely a result of analgesic effects [63]. Low birth-weight piglets also benefit from treatment of the sow and show better growth than the control group [65].

2.2.3 Postpartum Dysgalactia Syndrome (PPDS) and Mastitis-Metritis-Agalactiae syndrome (MMA)

Post-parturient disorders are reported worldwide, but subsumed under different terms, mainly depending on geographical location. While MMA is the commonly used name in European countries, PPDS (or PDS) has become widely accepted in English-speaking areas. Classically, it is perceived as part of the MMA complex, but PPDS should instead be considered the broader pathology. Essentially, the MMA complex is a subtype of PPDS, the most severe form clinically, but also the least common [30]. In the current review, both terms will be used, depending on the term used in the original article.

Friton et al. recognised that the three signs indicated by the term mastitis-metritis-agalactia syndrome are unlikely to occur together and that hence the term postpartum dysgalactia syndrome has been adopted [18]. Although metritis is often a part of the syndrome, mastitis is the central symptom [67].

Post-parturient disorders, including dysgalactia in sows, form an economically very important disease complex [68]. At farm level, the incidence of PPDS is estimated to differ between 0.5% and 60% [69], with an average incidence of 13% in pluriparous and 4.2% in primiparous sows [70]. In the Merck Veterinary Manual an incidence of 15 - 20% is reported [30].

PPDS is a primary cause of neonatal problems such as diarrhoea, crushing and poor growth. The syndrome is difficult to characterize because of its multiple manifestations and the difficulty in establishing the aetiology. PPDS is seen almost exclusively within the first three days after farrowing. Management factors are related to the incidence of PPDS; herds with a high PPDS prevalence are reported to have more interventions during parturition and administer more injections to sows and piglets. [30].

Puerperal septicaemia and toxaemia

Puerperal septicaemia and toxaemia is one of the many disease complexes described within PPDS. It is believed that gram negative bacteria, in particular Escherichia coli, are important in the aetiology of this disease. Evidence suggests that lipopolysaccharide (LPS) endotoxins, a portion of the cell wall of all gram negative bacteria, play a role in some cases. When endotoxins enter the blood stream endotoxaemia is a fact. These toxins suppress the release of prolactin, decrease the circulating amount of thyroid hormone, and increase the cortisol concentrations. Prolactin is the main hormone involved in the initiation of lactation.

Septicaemia and toxaemia lead to pathologies of susceptible organs like the uterus and the mammary glands and adversely affect production and the secretion of colostrum and milk. For the piglets the impact of the resulting insufficient energy supply and immunoglobulin ingestion can be enormous [30].

Mastitis-Metritis-Agalactia syndrome (MMA)

MMA is a multifactorial disease, occurring on most breeding farms. On average 20% of the sows is affected. The syndrome develops within the first two to four days postpartum and is typically accompanied by significant milk production failure. Clinical signs can include an increased rectal temperature (>39.3°C), loss of appetite or low water intake, redness and inflammation of teats, pain, failure to expose teats and nurse, and sometimes vaginal discharge [71]. Mastitis is a clear pathological entity; infected glands typically show signs of inflammation such as severe oedema and skin congestion [72], and, with many glands involved, sows develop fever (>40.3°C) and lose their appetite [73].

In addition to the acute effects in the sow, an important effect of the disease occurs in the piglets. In their first days of life, piglets are totally reliant on the sow for access to colostrum and milk. Every alteration in both milk yield and composition has a high impact on weight gain and growth rate [74]. As a result of hypogalactia or even agalactia

the economic performance and the number of weaned piglets per sow per year will be reduced [72].

Although the aetiology and route of infection are still matters of discussion, it is generally accepted that enterobacteriaceae, particularly Escherichia coli, are the most important cause for MMA. Beta-haemolytic streptococci and other coliform organisms have also been associated with the condition. The subsequent production of endotoxins triggers the systemic signs of the disease [75].

Subclinical MMA and Porcine Hypogalactic Syndrome (PHS)

Although MMA can be considered a common postpartum disease, subclinical mastitis in sows is often overlooked. The obvious signs may be absent, but the impact on production parameters of the offspring is significant. Clinical MMA appears to be only 'the top of the iceberg', since the majority of mastitis cases remain subclinical. A Spanish field trial revealed that even at farms with good management practices and no obvious clinical MMA syndrome, subclinical mastitis could influence the milk production of sows negatively. This can result in higher pre-weaning mortality, slower piglet growth and piglets with a lower body weight at weaning. Post-farrowing complete agalactia is not often seen in sows with MMA; however, decreased milk production following inflammation in some mammary glands is a common clinical sign. Standard antimicrobial therapy as single therapy is in these cases usually not very effective [76].

Treatment of PPDS and associated disease complexes

The treatment of choice for the diseased sow is antimicrobial and/or anti-inflammatory treatment; treatment must ensure adequate mammary gland function to sustain piglet growth. Systematic treatment of sows with meloxicam significantly reduced pre-weaning mortality, improved litter weight gain and improved piglet weight at weaning [71]. In low birth weight piglets from sows with subclinical MMA, the use of meloxicam resulted in higher increases in pre-weaning average daily weight gain and the proportion of piglets reaching the expected weight at weaning [77, 78].
NSAID treatments have a beneficial effect on the health of the affected sows [72]. Treatment strategies usually consist of one treatment on the day of parturition and sometimes a second treatment on day two (flunixin, tolfenamic acid) or day three (meloxicam) [4, 79].

Much research has been done on the efficacy of meloxicam in addition to antimicrobial and sometimes oxytocin therapy in sows suffering from puerperal septicaemia and toxaemia. The effects on sows and the productivity of their offspring were monitored. A bigger drop in rectal temperature of the treated sows, better daily weight gain of the piglets, and a higher weaning weight were proven by several authors [79, 80].

Revilla et al. found that mortality was similar between the meloxicam group and the placebo group, but the weight gain of piglets from the meloxicam-treated pigs was significantly higher (235 versus 219 g/day) and treatment increased the milk production [80].

In the study of Wagner et al. additional meloxicam treatment had no significant effect on sows suffering from puerperal septicaemia and toxaemia; the suckling piglets of the meloxicam group showed slightly more weight gain [81].

Revilla et al. suggest that early post-farrowing treatment of sows with meloxicam improves the survival and growth rate of piglets during the lactation period compared to an antibiotic therapy alone [76]. Apparently, meloxicam reduces the inflammation within the mammary glands, most likely via strong anti-endotoxin activity, enabling a better milk yield [76-78].
Following many efforts to optimise management factors, the prevalence of the clinical disease has substantially decreased, but managing the subclinical form still presents a challenge. Systematic treatment of sows post-farrowing with NSAIDs significantly reduced pre-weaning mortality, improved litter weight gain and improved piglets weight at weaning. Meloxicam treatment of sows led to higher piglet weights at weaning and a higher proportion of piglets reaching the ideal weaning weight. Routine prophylactic treatment of sows with NSAIDs post-farrowing should be considered, even at farms with no obvious clinical signs of MMA syndrome, because subclinical mastitis could cause significant losses in production [71].

Hirsh et al. compared the efficacy of meloxicam with that of flunixin, as an additional treatment to antimicrobial therapy and oxytocin. Differences in litter weight, daily weight gain and mortality rates were not significant between the groups. In piglets of diseased litters, however, the mortality rate was 50% lower in the meloxicam group [4]. In a preliminary field study in Spain, meloxicam administration to sows significantly increased the proportion of piglets reaching the expected target weight at weaning compared to flunixin meglumine when both products were being used in combination with an antibiotic [82]. A study by Lamana et al. also showed superior anti-inflammatory and anti-endotoxin efficacy of meloxicam when compared to flunixin meglumine. These authors showed that meloxicam was better in improving growth in piglets with a low birth weight, born from sows with MMA [77]. Meloxicam is also superior to tolfenamic acid for this indication [78].

2.2.4 Lameness

In a randomised double-blind, placebo controlled, multi-centre field study, meloxicam by intramuscular injection (0.4 mg/kg BW) has been proven efficacious for the treatment of non-infectious locomotor disorders in pigs. Behaviour score and feed intake improved with statistically significant differences in favour of meloxicam at all points after initiation of therapy. Significantly fewer pigs received a second treatment in the meloxicam group than in the placebo group. A ‘very good’ or ‘good’ clinical efficacy assessment was recorded in 83% of the meloxicam cases compared to 42% of the placebo controls at the final examination. Clinical lameness scores at rest and at walk improved significantly, resulting in a statistically significant improvement of the lameness [3].

2.3 Horses

2.3.1 The alleviation of inflammation and relief of pain in both acute and chronic musculoskeletal disorders

As a result of their anatomy horses are very prone to disorders of musculoskeletal origin. Disorders of the musculoskeletal system most commonly affect the horse's ability to move. How severely movement is impaired depends on the type and severity of the problem. Skeletal and joint disorders are the most common, but problems with the musculoskeletal system can also be an indication for diseases of the muscles, neurologic problems, toxins in the body, hormonal abnormalities, metabolic disorders, infectious diseases, blood and vascular disorders, poor nutrition and birth defects [30].

In the management of musculoskeletal disorders anti-inflammatories are often an important part of the recommended treatment. Anti-inflammatories reduce the amount of inflammation quite often associated with musculoskeletal disorders as well as pain.

Meloxicam is a commonly used [83] and potent [84] non-steroidal anti-inflammatory drug in equine practice. Research indicates that the administration of 0.6 mg meloxicam per kg body weight is an effective and safe treatment for the reduction of inflammation and relief of pain associated with lameness in both acute and chronic musculoskeletal disorders and soft tissue lesions [85, 86]. Early oral treatment with meloxicam ameliorates not only clinical signs and joint inflammation in acute synovitis, but may also limit inflammation-induced cartilage catabolism [83].

2.3.2 The relief of pain associated with equine colic

Colic is in the top three of most common disorders in horses and is the greatest cause of mortality in horses [87].

In its strictest definition, the term "colic" means abdominal pain. Over the years, it has become a broad term for a variety of conditions that cause a horse to exhibit clinical signs of abdominal pain. Consequently, it is used to refer to conditions of widely varying aetiologies and severity [30].

In most cases of colic, pain is mild, and analgesia is all that is needed. In these instances, the cause of colic is presumed to be spasm of intestinal muscle or excessive gas in a portion of the intestines. If, however, the pain is due to an intestinal twist or displacement, some of the stronger analgesics may mask the clinical signs that would be useful in making a diagnosis. For this reason, a thorough physical examination should be completed before any veterinary medicinal products are administered. However, because horses with severe colic or pain may hurt themselves and become dangerous to people nearby, analgesics often must be given first. Additionally, any horses with less severe problems may need pain relief until the other treatments have time to be effective. An analgesic that has the fewest adverse effects and that causes the least alteration in the horse's attitude should be selected. NSAIDs are used commonly to treat abdominal pain. Clinical experience suggests that flunixin meglumine may mask the early signs of

conditions that require surgery and, therefore, must be used carefully in horses with colic [30].

Research data have suggested that the intravenous administration of meloxicam may be a useful alternative to flunixine meglumine for postoperative treatment of horses with colic [88].

3. Conclusions

Meloxicam is a very effective and safe NSAID with proven anti-inflammatory, anti-pyretic and anti-endotoxin activity. The pharmacokinetic and pharmacodynamic properties of the molecule create the advantage of single dose efficacy; a single subcutaneous dose of meloxicam is as clinically effective as up to three consecutive daily intravenous doses of flunixin meglumine in cattle.

Besides rather specific COX-2 inhibiting effects and the lack of specific COX-1 inhibitory adverse events, meloxicam is also a potent inhibitor of oxyradical production at drug concentrations comparable with those encountered during therapy.
In many animal species and even in humans, meloxicam has proven its curative and supportive efficacy in many different diseases and situations, such as non-infectious locomotor diseases, respiratory infections, diarrhoea, mastitis, peri-parturient and painful procedures.

Cattle suffering from viral respiratory disease should only be treated with anti-inflammatory drugs. Primary or secondary bacterial infections will in many cases require antimicrobial therapy. The addition of meloxicam to this therapy will certainly improve the outcome and shorten the duration of disease. Viruses and bacteria induce a massively destructive inflammation in lung tissue, damaging the calf's growth potential permanently. The immediate and long-term positive effects of meloxicam have been shown in several studies.

The scientifically proven positive effects on production parameters when the product is used prior to castration of piglets and after parturition in sows cannot be ignored. Meloxicam does much more than inhibiting or decreasing pain; it is the anti-inflammatory activity that induces quick recovery of disease or surgical procedure and enables the optimal production capacity.

Dopharma's Melovem® 5 mg/ml was the first generic injection formulation containing meloxicam in Europe. With the addition of two new strengths, 20 mg/ml and 30 mg/ml, Dopharma now offers a complete range of injectable meloxicam preparations. The Melovem® 5 mg/ml is now mainly used in young animals, such as piglets, whilst for larger animals, such as sows and dairy cows, the Melovem® 20 mg/ml and Melovem® 30 mg/ml are much more ideal.

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