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PRODUCT REVIEW

Meloxicam in the Maintenance of Dairy Cow Productive Wellbeing

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About the reviewer

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This review discusses the detrimental effects of inflammatory conditions on dairy cow wellbeing and productivity and the use of the non-steroidal anti-inflammatory drug meloxicam in the management of mastitis and lameness in the context of long-term productivity. This article is supported by an educational grant from Boehringer Ingelheim Animal Health.

Mastitis in dairy cows

Mastitis, which, in most cases, is caused by bacterial pathogens, has negative effects on the health, well-being, longevity, milk production, and reproductive performance of dairy cows, leading to profit losses for dairy producers.[1,2]

The primary contributor to lower milk yields and a higher risk of culling observed in cows with mastitis is the mammary immune response and inflammation,[2] which leads to an elevated milk somatic cell count.[1] Clinical mastitis (mastitis with visible changes in udder and/or milk health) and sub-clinical mastitis (no visible changes but increased somatic cell count) were among the main reasons for cow wastage according to a bioeconomic modelling study conducted to determine the costs associated with different reasons for cow culling or on-farm mortality in a pasture-based seasonal system in New Zealand.[3] In this 2018 study, the total cost of cow wastage was estimated at $NZ23,628/100 cows per year, with 18% (or $NZ4,214/100 cows per year) of the estimated total being attributable to cow removals because of low milk production, udder problems, mastitis, or a high somatic cell count.

In terms of the effects of mastitis on the reproductive performance of dairy cows, a clear association between the incidence of mastitis and reproductive performance (including increased time to first service, services per conception, and pregnancy loss and reduced first service conception rate) has been demonstrated in a comprehensive meta-analysis.[4]

The annual global economic loss due to dairy cattle diseases has been estimated to be $US65 billion ($NZ106 billion using the average exchange rate in 2023), with clinical and subclinical mastitis together contributing to one-third ($US22 billion or $NZ36 billion) of total estimated annual global losses, based on an economic simulation that considered the global impact of 12 different types of cattle disease on milk production, fertility, and culling.[5] Across the 183 countries modelled, comorbidity-adjusted losses per cow were equivalent to average global losses of approximately $US12 per person-year ($NZ20 per person-year) in milk-producing countries, with the greatest mean per capita loss being in New Zealand ($US220 per person-year or $NZ359 per person-year).

Collectively, these findings emphasise the importance of taking steps to control mastitis to maximise dairy cow health and performance and economic return for farmers in terms of milk production and reproductive efficiency.

Mechanism of action of NSAIDs

Several species of bacteria have the ability to invade the mammary gland where they multiply and produce byproducts that stimulate inflammatory responses.[6] Increased levels of interleukin-1, tumour necrosis factor-alpha, and lipopolysaccharide induce production of cyclooxygenase (COX), the enzyme that catalyses the conversion of arachidonic acid to proinflammatory eicosanoids, including prostaglandins.[7,8]

Non-steroidal anti-inflammatory drugs (NSAIDs) act to prevent prostaglandin synthesis via the inhibition of COX, leading to anti-inflammatory, antipyretic, and analgesic effects.[9,10] The ensuing clinical benefits of NSAIDs include reduced body temperature, restoration of rumen motility, fewer signs of inflammation, and reduced sensitivity to pain.[9]

Meloxicam, which belongs to the oxicam class of NSAIDs,[11] has demonstrated analgesic, antipyretic, and anti-exudative effects in dairy cows with experimentally-induced clinical mastitis.[12]

Effects of meloxicam on udder health and milk production

With the pathophysiology of mastitis characterised by increased levels of inflammatory eicosanoids, potential benefits using of meloxicam in the management of mastitis in dairy cows have been investigated in several controlled clinical studies.[7,8,13]

In dairy cows with acute clinical mastitis (without systemic signs), meloxicam as monotherapy administered at the initial presentation of mastitis resulted in significantly ($p<0.01$) greater alleviation of udder discomfort compared to placebo in a randomised controlled clinical study.[13] There was little change in the milk yield of the

meloxicam-treated group before and after clinical cure, whereas the milk yield in the placebo group was significantly (p<0.01) reduced during the clinical phase of the disease compared to after clinical cure.

Meloxicam as an adjunctive treatment in the management of dairy cows with mild mastitis has been assessed under New Zealand conditions.[8] The addition of meloxicam to antibiotic therapy in dairy cows with mild clinical mastitis diagnosed during the first 200 days of lactation resulted in a significantly lower somatic cell count compared with antibiotic therapy alone (550,000 vs 711,000 cells/mL; p=0.001). The absence of an interaction between treatment and the number of days after treatment for somatic cell count indicated that the somatic cell count was consistently lower over time in the meloxicam-treated cows (**Figure 1**).

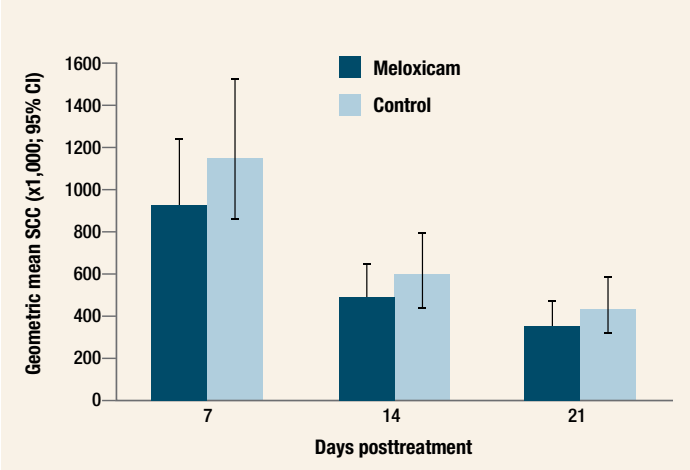

Figure 1. Somatic cell count for glands of cows with clinical mastitis at 7, 14, and 21 days after antibiotic therapy with meloxicam versus without meloxicam (controls).[8] Abbreviations: CI = confidence interval; SCC = somatic cell count.

In a subsequent clinical study that assessed the effects of adding meloxicam to antibiotic therapy in cows diagnosed with mild-to-moderate clinical mastitis within the first 120 days of lactation on European farms, a higher bacteriological cure rate was achieved in cows treated with meloxicam plus antibiotic therapy compared to antibiotic therapy alone (67.8% vs 56.3%).[7] Achieving bacteriological cure is an important factor in preventing the recurrence of clinical mastitis, which is associated with reduced milk yield and increased risk of culling and mortality.[14] The previous finding that use of meloxicam in the treatment of clinical mastitis resulted in a lower somatic cell count under New Zealand conditions was not replicated in the subsequent European-based study. This was attributed to differences between the two studies in terms of farming systems and pathogen distribution and there being no difference between the meloxicam and control groups in the proportion of glands that were uninfected following treatment in the subsequent study.[7]

The potential economic benefits of using adjunctive meloxicam in cows with mastitis have also been studied.[15]

Milk yield was estimated in a simulation study that modelled reproductive and productive outcomes in dairy cows to determine whether the addition of meloxicam to standard treatment for mastitis would result in a net positive economic benefit to farmers.[15] In dairy cows with mild-to-moderate clinical mastitis diagnosed in the first 120 days of lactation, the modelling demonstrated that non-pregnant cows treated with meloxicam plus antibiotic therapy produced more milk than non-pregnant cows that received antibiotic therapy alone (8,422 vs 8,350 kg of milk per lactation). Counterintuitively, the economic return on milk sold was slightly higher (€42 per mastitis case per year or $NZ67 per mastitis case per year using the average exchange rate in 2017) in the no-meloxicam treatment scenario (€2,562 vs €2,520/mastitis case per year or $NZ4,066 vs $NZ3,999/mastitis case per year). However, the no-meloxicam scenario had a higher proportion of non-pregnant cows (25% vs 12%) and non-pregnant cows had higher returns on milk versus pregnant cows in both treatment scenarios. The higher returns on milk production for non-pregnant cows were due to these cows remaining in production until culled.

Mastitis and reproductive performance

Reproductive efficiency, which is critical to dairy farm profitability, is negatively affected by mastitis.[6,16] Increased days to first insemination, increased services per conception, increased incidence of pregnancy loss, and decreased pregnancies per insemination at first insemination have all been linked to mastitis.

A prospective study that assessed associations between the frequency and severity of mastitis in dairy cows during a defined risk period (-3 to 32 days after first service) demonstrated that mastitis was associated with a lower probability of pregnancy,[16] with the odds of pregnancy being significantly reduced for cows with subclinical mastitis (odds ratio [OR], 0.75; p=0.031), clinical mastitis (OR, 0.67; p=0.012), and chronic clinical mastitis (OR, 0.56; p=0.029) compared to healthy cows. In addition, increased severity of clinical mastitis during the breeding risk period was associated with decreased odds (p=0.004) of pregnancy after first artificial insemination.

Mastitis has also been found to impair the reproductive performance of lactating cows in a study that assessed the effects of mastitis during early lactation on the reproductive performance of dairy cows.[6] The number of days to first insemination were significantly higher in cows that exhibited either clinical or subclinical mastitis before first insemination compared with animals that were uninfected or exhibited mastitis after confirmation of pregnancy (75.7 vs 67.8 days; p=0.01). Subclinical mastitis was equivalent to clinical mastitis in terms of its detrimental effects on other parameters of the reproductive performance of lactating cows.

In a study that analysed the reproductive performance of high-producing cows with clinical mastitis during the first 150 days of lactation, the number of days to conception in cows with clinical mastitis before (113.7 days) and after (136.6 days) first artificial insemination was significantly (p<0.01) greater than that for control cows without mastitis and that for cows that developed clinical mastitis after confirmation of pregnancy (92.1 days).[17] In addition, cows with clinical mastitis between first artificial insemination and conception required an additional insemination, had a longer breeding period, and had a higher number of days to conception compared to cows without clinical mastitis or that developed mastitis after being confirmed pregnant. Luteolysis, subsequent loss in progesterone, and early embryonic death were suggested as likely contributors to the impaired reproductive performance in the cows with mastitis.

A subsequent study assessing the association between clinical mastitis and abortion during early gestation in lactating dairy cows found that those that developed clinical mastitis during the first 45 days of gestation had a 2.7-fold higher risk of abortion within the next 90 days than cows that did not develop mastitis.[18]

Effects of meloxicam on longer-term productive wellbeing

Alteration of the ovarian structure (reduction of the vascular bed and an increase in fibrotic tissue) and reduced levels of GDF-9 (growth and differentiation factor-9) have been observed in cows with chronic mastitis.[19] The negative effect of mastitis on these essential factors of folliculogenesis partly explains the detrimental effect of mastitis on dairy cow fertility. Reproductive failure was the primary reason for cow wastage in the bioeconomic modelling study that determined the costs associated with different reasons for cow culling or on-farm mortality in a pasture-based seasonal system in New Zealand.[3] Reproductive failure accounted for 31% (or $NZ7,279/100 cows per year) of the total cost of cow wastage in 2018, which was estimated at $NZ23,628/100 cows per year.

In the study that assessed the effects of NSAID use in the management of mild clinical mastitis in dairy cows under New Zealand conditions, the addition of meloxicam to standard antibiotic therapy resulted in significantly fewer meloxicam-treated than control cows (antibiotic therapy only) being culled from the herd (16.4% vs 28.2%; OR, 0.42; p<0.001) [**Figure 2**], including significantly fewer meloxicam-treated than control cows being removed for failing to conceive (3.4% vs 8.4%; OR, 0.37; p=0.02).[8] These results suggest that meloxicam added to antibiotic therapy of dairy cows with mild mastitis is associated with a reduced risk of removal from the herd and that this may be, at least in part, due to a reduction in cows that fail to conceive.

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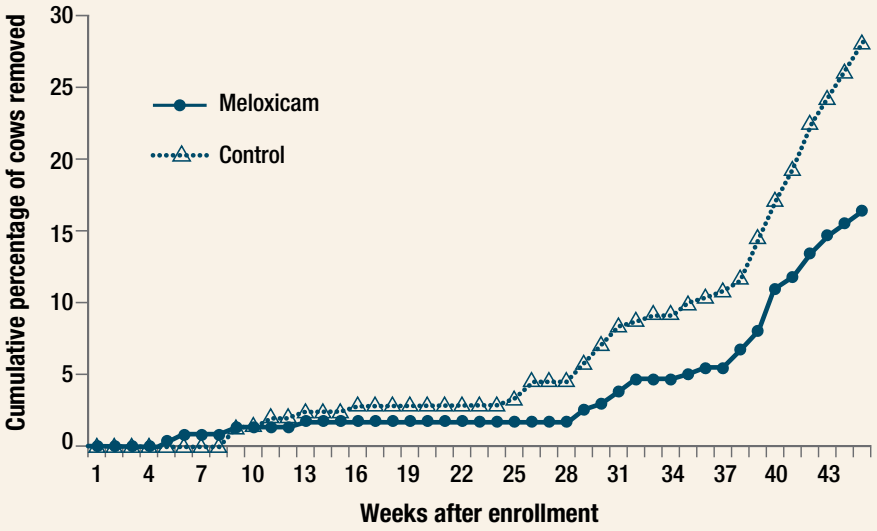

Figure 2. Proportion of cows with mild clinical mastitis culled from the herd during a 45-week period after receiving antibiotic therapy with meloxicam or without meloxicam (control).[8]

This suggestion was confirmed in the study that assessed adding meloxicam to antibiotic therapy for mild-to-moderate clinical mastitis in cows on European farms, as the proportions of cows achieving conception at first service (0.31 vs 0.21; p<0.01) and pregnancy by 120 days after calving (0.40 vs 0.31; p<0.001) were both significantly higher in meloxicam-treated than in non-meloxicam-treated cows.[7] Additionally, significantly fewer inseminations were required per pregnancy than in meloxicam-treated cows (2.43 vs 2.92; p=0.009).

A European simulation modelling study was conducted to assess whether the improved reproductive performance achieved by adding meloxicam to antimicrobial therapy for cows with clinical mastitis would result in a positive net economic benefit for farmers.[15] The model showed that parameters of reproductive performance in cows diagnosed with mild-to-moderate clinical mastitis in the first 120 days of lactation were better in meloxicam-treated cows than in non-meloxicam-treated cows: a shorter calving to conception interval (132 vs 143 days), a shorter inter-calving interval (405 vs 416 days), and fewer inseminations per conception (2.9 vs 3.6) compared with meloxicam alone. The percentage of cows culled for fertility reasons was also lower in the meloxicam-treated cows (12% vs 25%). Overall, the average net economic benefit was marginally higher (€42 per mastitis case per year or $NZ67 per mastitis case per year using the average exchange rate in 2017) with meloxicam treatment, primarily due to better reproductive performance and consequently less fertility-related culling.[15] Furthermore, sensitivity analyses showing that the economic benefit persisted across a range of technical and economic inputs suggests that adjunctive use of meloxicam is likely to be cost effective in multiple production system types.

Lameness in dairy cows

Lameness is a painful multifactorial condition in dairy cows that has significant welfare and productivity implications.[20,21]

Lameness in cattle increases the sensitisation to mechanical stimuli producing allodynia (increased sensitivity to non-noxious stimuli) and hyperalgesia (increased response to a painful stimulus).[22] This is both a peripheral effect with tissue injury causing the release of neurotransmitters and inflammatory mediators, which reduce the threshold of the local nociceptors,[23] and a central one as lameness can produce a marked increase in levels of inflammatory cytokines in the dorsal horn of the spinal cord,[24] which are thought to produce an exaggerated nociceptor transmission and pain amplification.

Chronic painful lameness negatively affects dairy cow welfare, and leads to reduced milk production and reproductive performance and hence increased risk of early culling.[20,25,26] A key mechanism by which lameness reduces reproductivity is its negative effect on fertility at all stages of the reproductive cycle.[20] For example, lame cows are slower to resume normal postpartum activity, show less intense heats, and less likely to ovulate than their non-lame counterparts.[27] In a prospective cohort study that assessed the effect of clinical lameness on the hazard of conception after the planned start-of-mating date under New Zealand pasture-based systems,[20] the daily hazard of conception for lame cows was reduced by a factor of 0.78 compared with non-lame cows and lame cows took 12 days longer to get pregnant compared with non-lame cows.

In terms of the economic impact of dairy cow lameness, researchers who quantified annual global economic losses due to 12 different dairy cattle diseases estimated that lameness accounted for $US5.5 billion (or $NZ8.97 billion using the average exchange rate in 2023) of total global annual losses of $US65 billion (or $NZ105.95 billion).[5] In terms of average comorbidity-adjusted losses per cow, lameness contributed an estimated $US30.50 (or $NZ49.72) per cow to total losses of $US351.50 (or $NZ572.95) per cow.

Effects of meloxicam in managing lameness

Pain in cows with lameness can be alleviated by using a multimodal approach involving corrective claw trimming and placement of foot blocks in combination with analgesic pharmacotherapy.[21]

With improved production outcomes having been demonstrated with the use of NSAIDs in the management of mastitis, use of NSAIDs could potentially contribute to improved reproductive performance in lame dairy cows and hence a reduced risk of culling.

The effect of providing anti-inflammatory effects using meloxicam at the time of lameness treatment for hoof-horn (HH) lesions in dairy cattle on time to lameness soundness after claw trimming and foot block application as well as on reproductive success has been assessed under New Zealand conditions in a randomised controlled study.[28] The addition of meloxicam to standard treatment significantly improved reproductive outcomes in dairy cows with farmer-identified lameness due to HH lesions compared to lame animals that did not receive meloxicam. Lame animals that received meloxicam had 2.37-fold higher odds of pregnancy at the end of the breeding period (p=0.019), 1.87-fold higher odds of being pregnant at the end of the first 6-weeks of breeding (p=0.037), and 1.42-fold higher hazard of conception (p=0.02), despite no apparent difference in time to lameness soundness. The investigators concluded that their study ". . . provides strong evidence of the positive effect of NSAID as part of the treatment of HH lameness, and that such positive benefits can present themselves months after the lameness episode".

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EXPERT'S CONCLUDING COMMENTS

The pain and inflammation associated with lameness and mastitis have a significant impact on the welfare of affected dairy cows. Thus, both conditions benefit from treatment with NSAIDs. Meloxicam is an NSAID with proven efficacy in cattle that has significant long-acting analgesic and anti-inflammatory effects and thus should always be considered as part of the treatment regimen for cows with lameness and mastitis. However, as the studies reported in this review show, meloxicam has significant long-term benefits beyond simply ameliorating the pain and inflammation associated with lameness and mastitis.

In cows with mastitis and lameness, treating with meloxicam can improve reproductive performance compared to cows that are not treated. These effects are not small, biologically unimportant effects but large effects with significant economic benefits. In the European study,[15] treatment of cows with mild-to-moderate mastitis with meloxicam resulted in large increases in first service conception rate and reductions in services per conception. Perhaps the most spectacular effect in the European study was that the percentage of cows culled for infertility in the meloxicam-treated cows was half that of the untreated cows.[15] Similar reductions were seen in the New Zealand study in the proportion of cows culled for failure to conceive, with overall culling rates in cows with mastitis being reduced by almost 60% by treating with meloxicam.[8] The recent New Zealand study in lame cows confirms that such benefits are not only seen in cows with mastitis – with meloxicam treatment resulting in a 30% increase in 6-week in calf rate and a halving in the proportion of cows empty at the end of the breeding season.[28]

We do not fully understand the pathophysiological process behind these benefits of meloxicam but these are large-scale well-planned studies which clearly show that meloxicam treatment has benefits on the reproductive axis. The principal reason for using NSAIDs in lame cows and in cows with mastitis still remains their immediate analgesic and anti-inflammatory effects but these findings show that there are benefits beyond these effects.

TAKE-HOME MESSAGES

- Mastitis and lameness in dairy cow herds adversely affect milk production and reproductive performance resulting in an increased risk of culling.
- The economic burden of both mastitis and lameness is considerable and is greatest for mastitis.
- NSAIDs, including meloxicam, can help to relieve the inflammation and pain associated with mastitis and lameness.
- In a randomised controlled clinical study, meloxicam monotherapy was associated with increased recovery of milk yield after healing and greater alleviation of udder discomfort in cows with acute clinical mastitis.
- Controlled clinical studies and modelling studies have demonstrated that adding meloxicam to standard therapy for mastitis in dairy cows resulted in:
  - A lower somatic cell count and higher bacteriological cure rate.
  - Improved reproductive performance via higher conception rates, reduced risk of culling, and fewer inseminations per conception.
  - A potential net economic benefit for farmers.
- In a randomised controlled study, meloxicam added to standard treatment for lameness in dairy cows significantly improved reproductive outcomes.
- Current evidence indicates that meloxicam has a role in helping to improve animal welfare and minimising the longer-term negative economic impacts due to mastitis and lameness in dairy cows.

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