Assessment and Management of Pain in Dairy Cows with Clinical Mastitis

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KEYWORDS

• Mastitis • Assessment of pain • Management of pain • Perception of pain • Treatment • Non steroidal anti-inflammatory agents

KEY POINTS

- Mastitis is a common and economically important problem. One of the major costs may be related to dairy cattle welfare, which remains largely unexplored.
- Pain is an unpleasant sensory and emotional experience associated with tissue damage. It is highly variable and difficult to quantify in dairy cattle.
- Both producers and veterinarians perceive severe clinical mastitis as being very painful but have varying views on the pain involved with mild and moderate cases.
- The public is concerned that the animal is feeling well, functioning well, and can live according to its nature, in addition to it having the five freedoms of animal welfare.
- Observations of both physiologic and behavioral changes should be considered when monitoring for disease.
- Behavioral responses related to pain and discomfort may include changes in activity, gait, mental state, vocalization, and posture.
- Novel tools for assessment of behavior include pedometry and position data loggers, weight distribution scales, pain pressure algometer, laser nociception tests, and rumination monitors.
- There is clear benefit to the use of nonsteroidal anti-inflammatory drugs for management of inflammation and alleviation of pain.
- Research conducted on lipopolysaccharide-induced, experimental-challenge models, and naturally occurring clinical mastitis cases has shown considerable benefit for pain management therapy.

INTRODUCTION

Despite the widespread implementation of mastitis control programs, clinical mastitis is a commonly occurring, and economically important, disease for the worldwide dairy

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industry.[1] In recent years, there has been a general decline in the incidence of clinical mastitis.[2] However, with an incidence rate of 23 cases per 100 cow years in Canadian herds,[1] a focus on research and extension on this issue is still greatly needed. Mastitis can be attributed to an annual economic loss of approximately $400 million for dairy producers in the United States.[3] Economic costs associated with mastitis include milk production losses, treatment costs, and potential long-term damage to the mammary gland as a result of inflammation.[3] Indirect costs from mastitis can include somatic cell count (SCC) penalties and increased culling rates.[4] In Britain, mastitis has been documented to be the leading cause of premature culling in dairy cattle.[5] In addition, an association between clinical mastitis and reduced reproductive performance in lactating dairy cattle has been reported; cows with clinical mastitis prior to being confirmed pregnant showed increased days to first service, days open, and services per conception.[6,7] In summary, clinical and subclinical intramammary infection is a major issue for the dairy industry, with broad-ranging impacts and consequences.

With the state of our knowledge on mastitis and its effects, it is understandable that intensive research has been conducted on the clinical, physiologic, immunologic, and molecular changes associated with mastitis. As such, our understanding of the biology and epidemiology of mastitis in dairy cattle has increased exponentially. Despite this increase in understanding, the effects of mastitis on cow behavior and welfare remain largely unexplored.[8] A wide variety of tools and techniques are now available and validated for the assessment of animal behavior and welfare. However, the assessment of pain due to mastitis has not been adequately studied. Many researchers contend that animals suffering from mastitis have compromised welfare and are in need of supportive pain management therapy.[8] Furthermore, some authors have asserted that appropriate analgesic treatment of clinical mastitis, to provide relief from suffering caused by pain, discomfort, and distress, should be mandatory.[9] Several nonsteroidal anti-inflammatory drugs (NSAIDs) are available as supportive therapies for clinical mastitis, even though documented evidence of efficacy and regulatory approvals for treatment of clinical mastitis are very limited.

This review will focus on our general understanding of pain, valid methods of assessment of pain in dairy cattle, as well as the state of our knowledge concerning the assessment, therapy, and effects of mastitis on cow behavior and welfare. Finally, the potential for increasing our knowledge in this area, through the incorporation of measures of cow behavior and welfare into mastitis research, will be discussed.

WHAT IS PAIN?

Pain is a term generally associated with human experience. This term is relatively subjective in context, depending on the individual's experience. The International Association for the Study of Pain defines *pain* as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[10] This definition is extremely broad and open to interpretation. Individuals can construe pain in many different ways, making it extremely difficult to characterize. For example, humans can verbally describe their pain, while we rely on behavioral and physiologic reactions from animals to determine if they are experiencing pain. Furthermore, there are differences in pain responses between species, between individual animals, between different disease stages, and between acute versus chronic conditions. As such, defining pain can be a controversial problem.

Perception of Pain in Dairy Cattle

Cases of clinical diseases, as seen with severely lame cows or severe clinical cases of mastitis, are extremely easy to characterize as being painful.[11] In such cases, the animal shows visible signs of pain and discomfort, including depressed appearance, decreased milk yield, weight loss, and abnormal postures, to name a few.[12] On the other hand, mild and moderate cases of clinical disease are not as easily characterized as being painful.[11] Unfortunately, the mild and moderate cases of disease occur at a substantially greater frequency. Thus, there is considerable potential for a large number of animals to be experiencing pain that may be overlooked. In most cases, it is a lack of understanding of the behavioral changes indicative of animal pain. As previously mentioned, the assessment and detection of pain can be extremely difficult and are complicated by the stoic nature of dairy cattle.[11] This situation is exacerbated in that from an evolutionarily perspective, cattle are considered a prey species and are predisposed to avoid showing pain and vulnerability, even when exposed to harmful stimuli.[11,13] Although modern dairy production systems do not expose cattle to any forms of predation, the herd dynamic of a free-stall facility can provide an opportunity for similar behavioral responses. In other words, the expression of pain could result in a more dominant animal causing restriction from access to feed and optimal housing areas.[14] In these situations, pain can be extremely difficult to identify and characterize.

Dairy Producers' Perception of Pain in Dairy Cattle

In Norway, a pain assessment instrument was administered as a questionnaire using a visual analog scale. It was completed by 149 dairy producers to evaluate their opinions on pain associated with various conditions in dairy cattle.[15] It was found that a large proportion of the producers surveyed did agree that animals do experience physical pain (70%). Yet, there was a wide range of pain scores allocated for the 21 conditions presented, ranging from 2.4 to 8.6 (on a 10-point scale). Severe clinical mastitis received a score of 7.6, which was in the same range as conditions such as dystocia and distal limb fractures in calves. However, moderate clinical mastitis with clots received a score of 5.7, which was similar to eye infections and laminitis. It is evident that several factors about a disease can influence a producer's opinion on how much pain an animal is experiencing.

Veterinary Practitioners' Perception of Pain in Dairy Cattle

The attitudes and approaches of animal health professionals toward the recognition, prevention, and alleviation of potential causes of reduced animal welfare have been explored to identify how animals are being treated in the dairy industry. For example, at a veterinary conference in Scotland, clinicians were administered a survey on the subject of dairy cattle welfare.[16] It was found that 68% of the respondents identified that it would be useful to have a validated scoring system for pain in cattle. These respondents also indicated that mastitis was not as painful as other clinical conditions or procedures, such as castration, cesarean section, or lameness. Yet, it is noteworthy that the greatest variation among respondents was with respect to mastitis. It was concluded that the numerous causative agents involved, the range of environmental conditions, and the varying levels of severity of infection that occur with cases of clinical mastitis may have been responsible for the wide range in response.[16]

A larger survey performed in the United Kingdom was used to assess the attitudes of cattle veterinarians on the use of analgesics, and on pain in general.[17] The respondents were questioned about the severity of pain associated with a variety of cattle diseases, including mild clinical mastitis and severe endotoxic *Escherichia coli* mastitis. On a 10-point scale, respondents rated severe mastitis at a pain level of 7, comparable to a fracture or foot abscess. On the other hand, mild clinical mastitis was rated at a severity score of 3, similar to hair loss from hock abrasion or left displaced abomasum. There was a significant difference between male and female respondents. Women rated many of the clinical conditions to be significantly more painful than the rating assigned by men. Interestingly, even though the veterinarians who were surveyed recognized that there was pain associated with even mild cases of mastitis, the use of analgesics for this condition was not suggested. Yet, it is well documented that veterinarians have a responsibility to the producers and their animals to prevent both the pain and distress that result in altered behavior and physiologic changes from an animal's normal state.[18]

Recently, a survey conducted by Thomsen and colleagues attempted to quantify the use of analgesics in cows and calves by bovine practitioners in Scandinavian countries.[19] The results indicated that younger veterinarians who graduated in the 2000s, in comparison to older graduates, were more likely to agree that recovery time is faster when analgesics are used. This result is understandable, considering the evolution of the teaching of pain management in veterinary medical education, especially over the past 10 to 15 years. Another important finding of this survey was the lack of difference between the attitudes of male and female veterinarians, which had been previously documented in the literature. It was speculated that this discrepancy could be due to an overall increase in awareness of changes in national legislation that encompasses the use of anesthesia and analgesia for common husbandry practices in Scandinavia.[19]

Public Perception of Pain in Animals

The increase in research on the behavior and welfare of dairy cattle can be attributed to many reasons. One of the primary motivating factors may be public perception. Various public media are focusing increased attention on the treatment, and overall welfare, of livestock. Scientists are encouraged to understand the behavior of animals and how to optimize management practices to decrease any stress and pain that they are experiencing.[20,21] There are 3 major questions that the public will ask when they are assessing the welfare of animals within a livestock industry:

1. "Is the animal functioning well?"
2. "Is the animal feeling well?"
3. "Is the animal able to live according to its nature?"

In regard to clinical mastitis in dairy cattle, it is probable that the answer to all of these questions is "no." As such, response to these questions may affect the opinions of the general public that clinical mastitis compromises the welfare of dairy cattle. In the consideration of the basic principles of animal welfare, there are the "five freedoms of welfare."[22] Mastitis interferes with 4 of the 5 freedoms. The first 2, "freedom from discomfort" and "freedom from pain, injury or disease," are common effects with most cases of clinical mastitis. To avoid this situation, mastitis should be detected and assessed quickly, and therapy should be provided in a timely fashion, so the welfare of these animals is not jeopardized. The "freedom from fear and distress" can also be compromised with cases of clinical mastitis. Finally, the fourth freedom, "freedom to express normal behavior" can also be applicable with clinical mastitis, since the environment in commercial dairy facilities restricts the opportunity for the animal to exhibit sickness behaviors, compared to a cow's natural environment. Given the dramatic effect that mastitis, and disease in general, has on cow welfare, it is important to identify and treat clinical mastitis cases as quickly and effectively as possible.

Research on Pain in Dairy Cattle

Recently, animal science and veterinary research has placed increased emphasis on animal welfare. Specifically, quantifying and alleviating the effects of painful surgery, husbandry procedures, and lameness have been the focus of most research involving pain in cattle. However, there is relatively little published literature aimed at determining the severity of pain linked with other specific cattle diseases, and at quantifying the importance of pain mitigation on animal welfare. An increasing focus has been placed on pain and distress exhibited due to management practices and how it impacts the animal's affective state.[21] These practices include dehorning and tail docking. As intervention procedures, humans performing these practices should easily identify when the animal is in pain and is suffering. In addition, recent emphasis has also been placed on the health and biological functioning of the animal, including acute diseases or injuries, such as lameness, transition diseases, and dystocia.[21] In response, it is clear that these issues receive the most attention in prospective research on welfare and pain, as they are of importance to the industry.

PHYSIOLOGICAL AND BEHAVIORAL CHARACTERISTICS ASSOCIATED WITH ILLNESS IN DAIRY CATTLE

Illness results in physiologic and behavioral changes in dairy cattle. Physiologic changes are extremely useful in the diagnoses of illness. Producers and veterinarians can monitor deviations from normal physiologic levels with considerable accuracy. However, the early detection of clinical disease by dairy producers may also be enhanced through the identification of behavioral changes. Therefore, the monitoring of both physiologic and behavioral characteristics should be considered when monitoring disease.

Inflammation and pain in animals are associated with neural, endocrine, hematologic, immune, metabolic, and behavioral changes that aim to restore homeostasis within the animal.[21] The immune system and the brain form a bidirectional communication network, whereby the immune system informs the brain about events occurring within the body. Through this communication network, initiation of a response by the immune system produces physiologic, behavioral, affective, and cognitive changes that are jointly termed "sickness" or "sickness behavior."[23] Sickness behavior is a sophisticated response to infection and inflammation. This sickness response is manifested by a number of distinct physiologic and behavioral changes, including loss of appetite, adipsia, increased thermoregulatory behavior, decreased social activity, somnolence, and changed grooming behaviors.[24] In addition, sick animals may experience malaise, an affective state that involves negative feelings of depression, anhedonia, pain, and lethargy.[23] Sickness behavior is not a maladaptive state. It is actually a highly adaptive response that acts together with the immune system to facilitate recuperation from both injury and illness.[23,25]

Physiological and Behavioral Indicators Associated with Mastitis in Dairy Cattle

To effectively treat clinical mastitis, it is important to have reliable methods for the detection and classification of severity of infection. The implementation of a clinical evaluation system, which incorporates both local and systemic signs of disease, has been found to provide the most sensitive and precise classification system for clinical mastitis, with very few false-positive results.[26,27] However, clinical mastitis is still most often detected at milking, by direct observation of the milk and mammary gland. Yet, as farm sizes continue to increase and available labor continues to decrease, dairy producers need to rely more heavily on automated systems, rather than visual detection. Less time is spent on the individual observation of each cow, and there is a greater risk of missing or misdiagnosing a mild or moderate case of clinical mastitis.

Mild and moderate cases of clinical mastitis cases have previously been studied, observing pain thresholds, altered stance, heart rate, respiratory rate, and rectal temperature in affected cows, compared with control cows.[28,29] It was found that animals with cases of moderate clinical mastitis had significantly higher heart rates, rectal temperatures, and respiratory rates compared to cows with cases of mild clinical mastitis and with normal cows. Cortisol levels and SCC were also significantly higher in cows with mastitis compared to normal cows.[28] Cows with both mild and moderate cases of mastitis had significantly larger hock-to-hock distances compared to normal cows, thereby indicating an altered stance.[29] These affected animals also exhibited an increased sensitivity to a mechanical pressure stimulus on the leg closest to the affected mammary quarter, suggesting a change in pain information processing as a result of inflammation. In general, in the case of moderate or mild clinical mastitis, it is more difficult to determine whether dairy cattle experience pain and reduced welfare compared with cattle with severe cases of mastitis. Due to their stoic behavior, it is also difficult to determine if NSAIDs would be beneficial to aid in recovery, and mitigate pain, during these less severe cases of mastitis.

With the difficulties of characterizing a case, and accurately identifying the initiation of illness, in cases of naturally occurring clinical mastitis, models have been developed to induce intramammary in dairy cattle. Recently, behavioral and physiologic effects of lipopolysaccharide (LPS) endotoxin-induced mastitis cases were examined in 20 lactating Holstein cows, randomly assigned to receive an intramammary infusion of either LPS endotoxin or saline.[30] Cows receiving the LPS endotoxin had higher rectal temperatures, serum cortisol levels, and peak milk SCC in the challenged quarter in the first 24 hours after infusion compared with saline-infused cows. In addition, endotoxin-infused cows spent reduced time eating, cud chewing, and lying in their stalls compared with saline-infused cows. Furthermore, rumen contractions were reduced in endotoxin-infused cows at sample times, which corresponded with peak rectal temperatures. Results of this study suggest that endotoxin-induced mastitis affects both behavioral and physiologic responses in lactating dairy cows.[30] These interesting findings support the need for more investigation of responses in experiments that utilize challenge models with mastitis-causing pathogens, as well as with naturally occurring cases of clinical mastitis. Yet, preliminary conclusions could be drawn that the behavioral and physiologic changes found with severe and moderate clinical mastitis are indicative of pain. Furthermore, it could be concluded that NSAID therapy could provide very useful anti-inflammatory and antipyretic activity for these cattle, along with an analgesic effect, that would result in substantially improved animal welfare.

OBJECTIVE ASSESSMENT OF DISTRESS AND PAIN IN DAIRY CATTLE

Chronic pain, as observed in cases of mastitis, is generally regarded as a pathologic process.[31,32] Recent research has focused on behavioral observations and assessing physiologic parameters to objectively define if an animal is experiencing pain or distress.[33] Although research-based equipment is an ideal method for assessing discomfort as precise indicators of pain, some of the more traditional measurements can be applicable on-farm. For example, the most basic indicators of illness or pain are decreased dry matter intake (DMI), water consumption and milk production.[34]

Since cows generally have relatively consistent intakes and production, a decline in either measure is a good indicator that there may be a problem. Similarly, changes in milk quality can also be an indirect indicator of inflammation and potential pain. An elevated SCC is usually associated with inflammation and tissue damage, which can be indicative of pain.[35] Another milk component that can be objectively measured is L-lactate dehydrogenase, which is an enzyme in the milk that increases due to mastitis.[36] A biosensor to detect this component has become commercially available and can predict the onset of infection before it actually becomes clinical.[37] In terms of physiologic parameters, acute phase proteins, such as serum amyloid A and haptoglobin, have also been shown to be good indicators of infection, stress, inflammation, and pain.[38] All of these parameters can be successful in assessing the pain associated with mastitis. However, one of the most effective, but frequently unused, methods of assessing discomfort is observing the overall behavior of the animal.[39] Behavioral responses related to pain and discomfort may include changes in activity, gait, mental state, vocalization, and posture. Some of these behaviors are reflexive, whereas others are manifested to decrease the occurrence of tissue damage, reduce the recurrence of tissue damage, and promote overall recovery.[39,40]

Pedometry systems are available for activity monitoring in the dairy industry and have been used for the detection of lameness, estrus, and other conditions. There are many commercial pedometry systems currently available. Systems with monitors attached to the leg, rather than the neck or body, produce the most accurate representation of lying behavior.[41] A field study in Israel revealed that 92% of cows that developed clinical lameness had a decrease in pedometric activity of at least 15%.[42] Conversely, estrus causes an increase in physical activity and can increase the pedometric activity of free-stall housed cows by 4-fold.[43] Evidence is accumulating that cow activity increases significantly in the period immediately prior to calving. It has been suggested that this increased restlessness may be a result of discomfort or distress.[44,45] Huzzey and colleagues observed that in the 3 days before calving in dairy cows housed indoors, the number of standing bouts increased by 80%.[44] With the development of automated recording of activity data and the development of algorithms for its interpretation, there is considerable potential for pedometry activity measurements to be a beneficial on-farm tool for the early detection of clinical mastitis and, in turn, help to mitigate potential pain in cattle.

There have been some new research developments that show considerable potential for assessment of pain in dairy cows. These measures are extremely precise and automated, to easily identify subtle changes in cow behavior that may accurately detect pain. For example, electronic data loggers that measure the orientation of the animal (recumbent or upright) can be used to monitor lying and standing behavior. Specific measurements include time spent lying, time spent standing, and the frequency of lying bouts and lying laterality that the cow exhibits. Significant changes in these behaviors, such as decreased lying times, and increased lying bouts, can be an early indicator of discomfort. Recent research in cows with endotoxin-induced clinical mastitis showed decreased lying time and increased lying bouts in these cases.[46]

In other recent research, specialized weighing platforms have been used to identify lameness in dairy cattle. This weight scale system has the ability to calculate the weight distribution on each hoof independently, allowing the identification discomfort in dairy cows.[47] Similarly, research conducted by Pastell and colleagues looked at weight distribution in cattle and its ability to detect lameness and other hoof care issues.[48] This measure was proved to be sensitive for the detection of lameness in cows, and particularly those suffering from sole ulcers. However, this method was not useful in detecting cases of mild lameness. Combined with the use of other tools, this technology has the potential of being an extremely useful indicator of discomfort.

The pressure algometer is another technology that has been shown to accurately measure pain. This instrument is used to exert and measure pressure on an affected body region, and determine the *pain threshold*, which is defined as "the minimum intensity of a stimulus that is perceived as painful."[10] The algometer has been used successfully in dairy cattle research, specifically after the procedure of dehorning,[49] and in cases of lameness caused by integument lesions.[50]

Changes in nociceptive thresholds have been observed in situations of acute stress. These thresholds can be measured using a laser-based method to detect thermal nociception.[51,52] *Nociceptive pain* is defined as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors."[10] In this method, a laser beam is focused on the animal's lower limb. A change of behavior in response to the laser, such as kicking or tail flicking, can be used to identify discomfort. Research suggests that the behavioral responses elicited in response to laser stimulation are both valid and reliable as an indication of nociceptive responses in the cow.[52]

A decrease in rumination has been shown to be a good indicator of discomfort in cows with cases of mastitis.[53] It is possible that monitoring rumination may provide a reliable measure of pain or systemic discomfort in cases of clinical disease. It has been determined that when dairy calves were intravenously infused with LPS endotoxin, there was a reduction in their total rumination time simultaneously with peak fever response.[54] Similarly, it has been reported that a reduction in rumination time was associated with increased cortisol levels in cattle.[55] Although visual detection of rumination has proven to be a good method to monitor rumination patterns, as with any subjective measurement, it can sometimes be difficult to detect changes solely from visual observations, which necessitates an automated device to measure rumination. A recent technologically advanced tool has been developed and validated and become commercially available for dairy farm use. This new tool, rumination HR Tags (SCR Engineers Ltd, Netanya, IL), is an enhanced version of an activity monitoring tag for the measurement of rumination and can be used for monitoring and detecting changes in the daily rumination of dairy cattle.[56] It is evident that there are many instruments that can be used by both scientists and producers to successfully evaluate the pain associated with disease, such as with clinical mastitis.

THE USE OF NSAIDS IN CATTLE

Treatment of inflammation relies on relieving the pain and other systemic effects that commonly accompany inflammation, and slowing any further tissue damage. NSAIDs are commonly used in animals to reduce inflammation (anti-inflammatory), reduce pain (analgesic), reduce pain sensitivity (antihyperalgesic), and decrease overall body temperature (antipyretic). These drugs act by inhibiting cyclooxygenase, which in turn prevents prostaglandin synthesis (**Fig. 1**).

Around the world, commercially available NSAIDs are approved for anti-inflammatory and antipyretic indications. The actual intended pharmacologic effect of NSAID administration has not been documented, meaning that the frequency of use of NSAIDs in cattle with an intention to mitigate pain is not well understood. One survey performed by the Colorado Veterinary Medical Association (Denver, CO) determined that approximately 50% of veterinarians use NSAIDs for pain management following surgery.[57] A Canada-wide survey was conducted to describe the use of analgesics in cattle. Of the 309 veterinarians who reported treating acute toxic mastitis cases, 93% of them provided analgesia in the form of ketoprofen or flunixin meglumine as

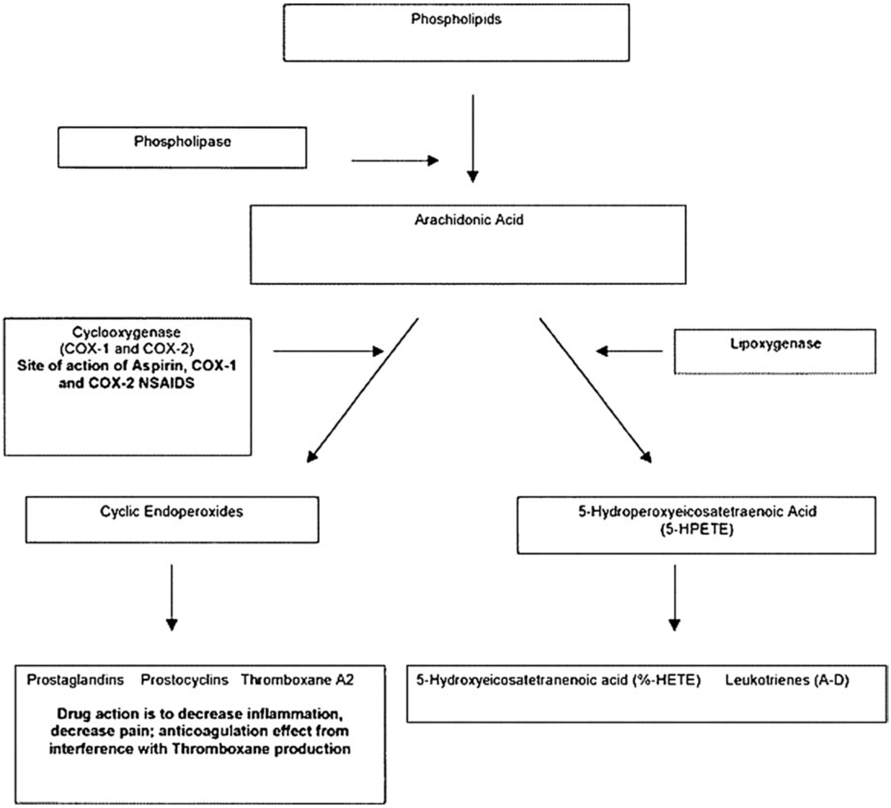

Fig. 1. The mechanism of action of NSAIDs. (*From* Summers S. Evidence-based practice part 1: pain definitions, pathophysiologic mechanisms, and theories. J Perianesth Nurs 2000;15:357–65; with permission.)

supportive therapy.[58] This Canadian study did not attempt to determine the distribution of use of analgesics in moderate versus severe clinical mastitis cases. It is noteworthy that of the 309 veterinarians questioned, 300 of them had graduated prior to 2001. Of those respondents, 27% had never participated in a continuing education program for pain management in animals. Yet, a large majority of the veterinarians that graduated prior to 2001 thought that their knowledge of pain management in dairy cattle was adequate. These veterinarians were asked to rank common dairy management procedures such as dehorning, displaced abomasum surgery, castration, toxic mastitis, etc, with respect to the amount of pain endured by the animal. None of the procedures were considered to be painless. It was therefore concluded that there is a need for continuing education opportunities for veterinarians with respect to pain identification and analgesic use in food animal species.[58]

A recent Canadian study evaluated the efficacy of a single administration of an NSAID at the onset of a naturally occurring case of neonatal calf diarrhea complex, in conjunction with oral rehydration therapy, and perhaps antibiotic treatment.[59] It was found that NSAIDs successfully reduced the behaviors associated with sickness and pain and significantly improved calf welfare. Calves treated with NSAIDs had a stronger appetite for milk during sickness, consumed more starter ration and water, gained significantly more body weight during the trial, and exhibited less pain-related behavior compared to calves that received placebo treatment.[59] Similarly, when investigating NSAID use for cases of induced diarrhea in calves, treatment with flunixin meglumine decreased the fecal output[60] and improved the clinical status[61] of treated animals. Bednarek and colleagues observed the use of NSAIDs in addition to antimicrobial therapy for calves with bronchopneumonia and found that there was an improvement in recovery rates with these treated animals.[62]

With the accumulated evidence, it is clear that there may be benefit to the use of NSAIDs for management of inflammation and alleviation of pain. As an example, research concerning the use of NSAIDs to manage pain in lame cows has been widely studied. By administering ketoprofen to lame cows, the resulting hyperalgesia was regulated on certain days following treatment, showing promising potential to reduce hyperalgesic effects.[63] Incorporating NSAID therapy into treatment protocols for a variety of clinical problems, including clinical mastitis, should improve the welfare of diseased animals and correspondingly decrease the economic losses to food animal producers.[64]

USE OF NSAIDs WITH CASES OF MASTITIS

Treatment decisions for animals with severe clinical mastitis most often involve veterinary intervention. Survey research has shown that both dairy producers and veterinarians generally agree that severe cases of mastitis can cause the animal significant pain and distress.[58] As such, it is common practice to provide the severely mastitic cow with NSAID therapy, in addition to antibiotics. Finally, there is mounting evidence for this use in both induced and naturally occurring cases of clinical mastitis, even though formal regulatory approval is rare.

NSAID Therapy in Cases of Endotoxin-Induced Clinical Mastitis

The use of NSAIDs has been shown to decrease rectal temperatures, decrease signs of inflammation, maintain rumen motility, and reduce heart rates in cows challenged with an intramammary infusion of LPS endotoxin to mimic early coliform mastitis compared with their nontreated counterparts.[30,65,66] Decreased heart rate could be interpreted as a result of a decrease in animal distress or alleviation of pain by the NSAID. There was also an observed reduction in fever of treated animals. As previously stated, fever is a strategy used by animals to combat infection. As such, it is unknown whether the reduction of fever is actually advantageous for animals with an early case of clinical mastitis. There is generally a lack of published literature supporting the beneficial or detrimental effects of reducing fever in these cases.

Milk measurements and behavioral activity was monitored to examine the effects of flunixin meglumine given 4-hour postinfection during endotoxin-induced clinical mastitis.[30] The frequency of rumen sounds were numerically increased in challenge animals, but DMI was not affected by the infection or treatment. The lack of difference in intake was likely due to the feeding management or the actual length of the infection time during the study. However, treated cows did show an increased eating time 9 to 12 hours after administration, as well as an increase in cud chewing compared to the nontreated control group. While infected cows spent less time lying in the first 12 hours after infection, flunixin treatment had no effect on the lying behavior.[30] This study was effective in showing the impact of flunixin administration against nontreated controls.

Ketoprofen is another NSAID used in the dairy industry.[11] Ketoprofen inhibits both of the cyclooxygenase pathways. The effectiveness of ketoprofen in experimental LPS-induced clinical mastitis cases has been evaluated. Three treatment groups were studied where 2 groups of experimental animals were inoculated with LPS and compared to an untreated group and served as the control group. The 2 groups of experimental animals were given ketoprofen either orally or intramuscularly 2 hours after LPS mastitis was induced.[67] Untreated control animals showed an increase in rectal temperature to an average of 40.5°C with differences between the groups seen at 6, 8, and 10 hours postchallenge. By 2 hours postchallenge, respiratory rates were increased. Yet, the respiratory rate–treated groups started to decline by 6 hours and were normal after 24 hours. Rumen contractions were reduced by 50% in the 2 hours postchallenge. But, within 6 hours, ketoprofen-treated animals began to recover, with full recovery by 24 hours; whereas the control group did not recover until day 7. As the udder of the animals was palpated, a visual analogue scale assessed the pain experienced. Ketoprofen allowed for a more rapid decline in pain scores compared to the untreated control. Further, milk thromboxane β_2 levels, an indicator of the general inflammatory status of an animal, were reduced at 6 hours postchallenge compared to 12 hours postchallenge in the control animals.

NSAID Therapy in Clinical Mastitis after Experimental Challenge

Anderson and Muir reviewed numerous articles concerning the use of NSAIDs in dairy cattle, which clearly demonstrated an improved response to treatment in affected animals after a variety of veterinary procedures.[18] These animals also returned to a normal physiologic state more quickly when an NSAID was administered prior to specific procedures. When cows were infused with *Escherichia coli* and given an NSAID prior to the development of clinical signs of infection, it was found that 2 NSAIDs almost entirely blocked febrile response and delayed the decrease in rumen activity of affected animals.[68] Other studies with experimentally induced coliform mastitis have also shown improved recovery in these treated animals.[69] Oral and intravenous NSAIDs provided equal systemic responses.[70] In a similar experiment, it was found that NSAIDs decreased mammary inflammation and rectal temperature but did not prevent milk production losses or appetite reduction.[71] In very recent research, the use of flunixin meglumine was evaluated during experimentally induced *E coli* mastitis.[72] It was concluded that *E coli* mastitis altered physiologic parameters, animal resting activity, DMI, and milk production, having a negative impact on animal well-being. There was improvement in DMI and milk production with flunixin therapy, providing evidence for using an NSAID as supportive therapy in alleviating the adverse effects associated with *E coli* mastitis.[72]

NSAID Therapy with Naturally Occurring Mastitis

The effect of NSAIDs on naturally occurring clinical mastitis is not well documented in the literature. As it is difficult to perform research on naturally occurring infections, most of the published literature reports on results obtained from experimentally induced infections. Both induced and naturally occurring infections result in increases in milk SCC, body temperature, and concentrations of tumor necrosis factor-α; mammary gland swelling; and a decrease in milk production.[73] Thus, there are many similarities between clinical symptoms for natural infections and experimentally induced infections. However, it may be inappropriate to directly compare cases of clinical mastitis resulting from LPS endotoxin infusion or even experimental challenge using live organisms with cases of naturally occurring mastitis. Early research in this area documented the administration of antibiotics and 1 intravenous treatment of NSAID at the time of first physical examination after the detection of severe endotoxic naturally occurring clinical mastitis.[74] These researchers found no difference in body temperature, milk production, or need for additional therapy between treatment groups, when monitoring animal responses every 24 hours.

Another early study evaluated the therapeutic usage of flunixin meglamine administered intravenously to animals with naturally occurring clinical mastitis, to determine whether cows with clinical mastitis suffered pain over time and if treatment with an NSAID would help with pain alleviation.[11] Cows with mild or moderate mastitis were given an NSAID, via either intramammary or intravenous route of administration. Pain thresholds were determined using a mechanical device that exerted pressure to the hind limb of each cow. Cows with mild and moderate cases of clinical mastitis showed a heightened responsiveness to pain that persisted for days or weeks after onset. The cows with mild clinical mastitis exhibited reduced sensitivity to pain when treated with an NSAID intravenously. A beneficial effect of the relief of pain was documented. However, similar results were not found with the moderate cases of clinical mastitis, which may have been attributed to the dosage of NSAID being too low. In addition, the observed pain relief by the NSAID in that study was short-lived, and it was recommended that repeated doses of intravenous NSAID might allow for more long-term pain relief.[11,75]

In a study in Israel, it was found that giving ketoprofen intramuscularly for 5 days allowed affected cows to return to 75% of their daily milk production recorded prior to their mastitis infection.[76] Upon initial diagnosis of clinical mastitis, the animals were given antimicrobials in combination with ketoprofen. A secondary portion of the study included ketoprofen treated versus a placebo-treated control group. The animals treated with ketoprofen had an average 93.5% recovery rate based on production parameters compared to the average recovery rate from the control groups of 78.4%. Furthermore, only 1 (3%) of 39 ketoprofen-treated cows were culled that lactation versus 9 (22%) of 41 control animals.

In another study, 100 dairy cows with both mild and moderate naturally occurring cases of mastitis were assessed for pain.[77] It was found that the respiratory rate, rectal temperature, and heart rate were all significantly higher in cases of moderate mastitis compared to mild clinical mastitis cases. Animals were administered the NSAID, meloxicam, in either a single- or a 3-dose regimen. Pain threshold levels were then measured. Animals treated with NSAIDs returned to their normal threshold levels for these outcome variables significantly faster than untreated animals. The effect was similar whether an animal received 1 or 3 doses of meloxicam. It was concluded that by promoting recovery of moderate or mild mastitis by alleviating pain associated with a case of mastitis, cattle welfare will be improved. Other studies that have treated cows with meloxicam have recorded the alleviation of pain and discomfort associated with mastitis, by reducing heart and respiratory rates and pain responses in lactating dairy cows.[78]

The use of NSAIDs for the treatment of mastitis has been most commonly prescribed for cases of severe endotoxic mastitis and has not been widely adopted as a standard treatment for cases of mild and moderate clinical mastitis. It is well recognized that for such cases, treatment decisions do not often directly involve veterinarians. Usually, the therapy of these cases at the time of their detection is up to the discretion of the dairy producer or farm manager. Farm personnel often follow a treatment protocol that is designed by both farm staff and the herd health advisory team. It is desirable to create a set of standard operating procedures as a treatment protocol for all cases of clinical mastitis, such as found with the Canadian Quality Milk On-Farm Food Safety Program,[79] and to consult with a veterinarian about how to carry these plans out efficiently. As such, there may be an opportunity for greater use of NSAID therapy in mild and moderate clinical mastitis cases.

In a field study conducted in New Zealand, treatment of mild and moderate clinical mastitis with a combination of meloxicam and a parenteral antibiotic (penethamate hydriodide) was evaluated for its effect on SCC, milk yield losses, clinical outcomes, and culling rates as compared with antibiotic therapy alone.[80] Cows were treated with 5 g of penethamate hydriodide daily for 3 days after the clinical detection of mastitis. Half of these cows were also treated with 250 mg of meloxicam and the other half were treated with a placebo vehicle (control group). It was found that there was no difference between treatment groups in the number of cows that were defined as treatment failures (ie, retreated within 24 days of initial treatment, died, or the treated gland stopped producing milk). There was also no difference in milk yield for the cows treated with meloxicam compared with the control cows. However, SCC was lower in the meloxicam-treated group compared with the control group after treatment (550 $\pm$ 48 vs 711 $\pm$ 62 $\times$1,000/mL, respectively) and fewer meloxicam-treated cows were removed from the herds (39 of 237 [16.4%] vs 67 of 237 [28.2%], respectively). It was concluded that treating cows with a combination of meloxicam and penethamate resulted in a lower SCC and a reduced risk of removal from the herd (culling) compared with the penethamate treatment alone.[80]

SUMMARY

It is clear that clinical mastitis has severe detrimental effects on the animal and negative economic impacts for dairy producers. However, pain associated with clinical mastitis, generally, is not measured and not treated. Attention to behavioral and physiologic indicators should be used to monitor animal health. New technologies may allow dairy producers to identify clinical mastitis in its very early stages, or even before clinical changes occur. Furthermore, automated measures of activity, such as step counts and lying time, show promise as predictors of clinical problems. These new technologies, in addition to other automated measures, have the potential for improving the screening methods for preclinical mastitis and accurately predicting the onset of a clinical mastitis event. With this opportunity for very early detection of infection, there is a potential for early intervention with NSAID therapy, which may allow for maximum efficacy from its use.

Despite which specific NSAID is used, it is clear that the benefits on temperature, rumen function, SCC, milk production, behavior, and pain sensitivity in animals during mastitis indicate that this therapy has a role throughout the dairy industry. As the health and well-being of dairy cattle continue to be scrutinized by consumer groups, it is essential that the alleviation of any perceived pain or discomfort associated with clinical mastitis should be addressed.

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