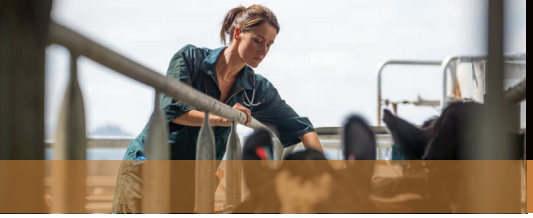


PAIN RELIEF IN NZ DAIRY COWS

Veterinarians have the opportunity to improve wellbeing and reduce inflammation and pain in dairy cows by using and authorising non-steroidal anti-inflammatories (NSAIDs). Additionally, use of NSAIDs will result in improved health outcomes and hence animal efficiency. This demonstrates better cow care and a more sustainable New Zealand (NZ) dairy farming industry, helping to meet the expectations of consumers of our dairy products.

The desired outcomes from the use of NSAIDs are:

1. Pain relief (analgesia)
2. Anti-inflammatory effect
3. Anti-pyretic (reducing fever)

The most common NSAIDs used in NZ dairy cows are ketoprofen and meloxicam. Both of these inhibit the COX-1 and COX-2 enzymes in the inflammatory cascade although meloxicam is more selective towards COX-2. Ketoprofen also has a direct pain relief (analgesic) action by inhibiting the inflammatory mediator bradykinin (Figure 1).

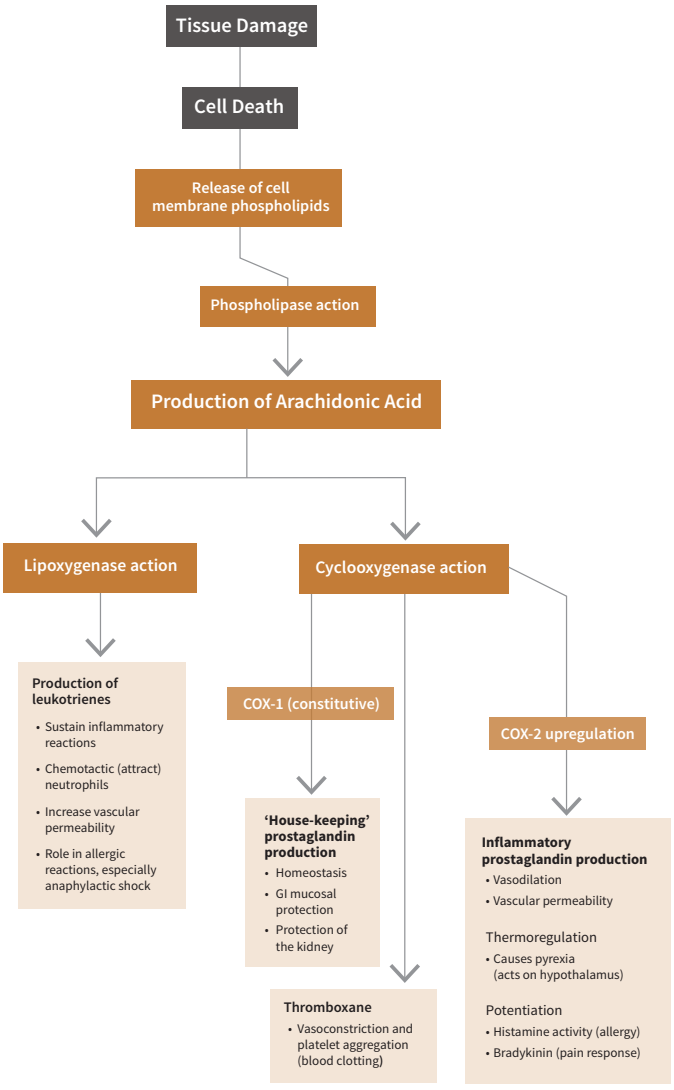


Figure 1. The inflammatory cascade

It is likely that for all available NSAIDs, the effective pain relief duration will be shorter than the anti-inflammatory effects. For example, meloxicam in cattle has an anti-endotoxin effect that lasts at least 50 hours[1] but post-surgical analgesia (e.g. following claw amputation) may not last longer than 24 hours[2]. This could be accounted for with different treatment frequency, for example, repeat daily dosing. When analgesic effects are important for animal well-being, daily NSAIDs such as ketoprofen may be advantageous as cattle can be treated on several consecutive days whereas meloxicam is only registered for a single dose.

Measuring pain in cows

There is no standardised pain model for cows. Both the physiological effects of pain (e.g. increased temperature, increased heart rate, swelling, loss of function) and the psychological effects (e.g. a lame cow has reduced feed intake due to reluctance in walking to access feed due to pain) need to be considered.

The physiological effects are easier to measure but have limitations. While indicators including cortisol levels have been used to indicate a pain response, this measurement is not always appropriate as an indicator of pain because increased cortisol can also be associated with stress of being handled or discomfort.[2,3]

It is becoming more common for researchers to measure the psychological effects of pain using behavioural observations, even though measuring this can be difficult due to the stoic nature of cows. As an example, cows with a clinical diagnosis that may be painful (e.g. mastitis, lameness) had a significantly higher score for 'attention towards the surroundings', 'head position', 'ear position', 'facial expressions', 'response to approach' and 'back position' than cows in a healthy control group, and treatment with ketoprofen significantly reduced these scores.[4]

Pain relief after surgery

Surgeries performed by veterinarians, such as claw removal, caesarean section or correction of a displaced abomasum, are painful procedures. While local anaesthetic improves animal welfare, and makes the procedure safer, the use of NSAIDs help manage pain during the recovery period. When an NSAID was administered to cows after abdominal surgery, cows flicked their tail less, spent more time lying on the side of the surgical site and had increased feed intake.[16]

Pain relief at calving

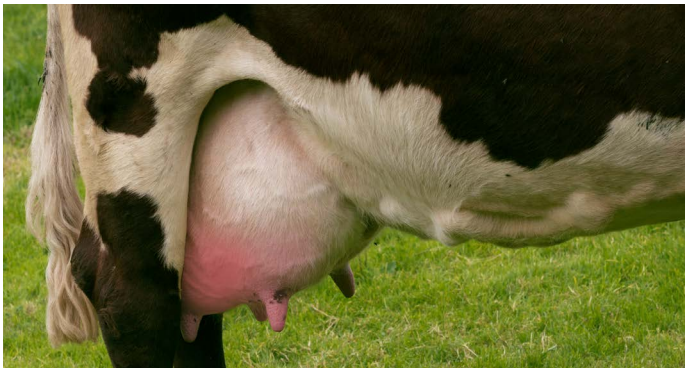
Pain relief (ketoprofen or meloxicam) administered to cows with dystocia at the time of calving has been shown to increase activity, increase feeding time and increase milk yield.[17,18,19]

Alongside pain incurred as a result of the calving process, it is widely believed that all cows experience some degree of systemic inflammation in the several days after parturition. The magnitude and persistence of the inflammatory state varies widely among cows. Several studies have linked the degree of postpartum inflammation to increased disease risk and decreased whole-lactation milk production.[20] Targeted use of NSAIDs during this window of time has enhanced whole-lactation productivity in several studies. In a Canadian study, cows treated with a single dose of oral meloxicam at calving produced 0.64 L/day more milk over the first 90–120 days in lactation, had 0.75 times the odds of subclinical mastitis at first herd test, and were culled or died at 0.46 times the rate before 60 days in milk relative to untreated controls.[21] These results are consistent with other research indicating that parturition is a painful and risky event for cows.

The choice of NSAIDs used at calving is very important. Flunixin meglumine is COX-1 selective and can significantly increase the risk of retained foetal membranes (RFM).[22] Meloxicam is known to be a preferential COX-2 inhibitor thus having a targeted action against inflammatory processes.[23] Meloxicam however incurs an 84-hour milk withholding period for treated cows, which can make it less desirable for dairy cows compared with NSAIDs that have a nil milk withholding period. Ketoprofen inhibits both COX-1 and COX-2, showing greater activity as a COX-1 inhibitor.
A study in the UK looked at the effects of ketoprofen treatment of dairy cows at calving.[24] Cows treated with ketoprofen at calving and again 24 hours later were 1.7 times less likely to incur an RFM compared to the untreated cows.

Pain relief for mastitis

Mastitis is inflammation of the udder, usually caused by a bacterial infection. Mastitis is painful and can reduce milk production and hence animal efficiency. The clinical signs of mastitis depend on the bacteria involved and the cow's immune response. Symptoms of acute clinical mastitis may include a hot, swollen udder and reduced appetite, while for mild to moderate mastitis the only symptom may be clots in the milk.



Mastitis caused by Gram positive bacteria

Most mastitis in NZ is caused by Gram positive bacteria (*Strep. uberis, CNS, Staph. aureus*). Treatment of acute mastitis with NSAIDs is clearly indicated from an animal wellbeing perspective. There is increasing evidence that even mild to moderate mastitis can be painful and that the use of NSAIDs has benefits. Cows with moderate mastitis have elevated temperatures, and greater hock distances when standing, indicating that it is painful.[6]

Treatment of NZ dairy cows with mild to moderate clinical mastitis (as diagnosed by the farmer) and treated with a combination of meloxicam and penethamate resulted in a lower SCC and a reduced risk of removal from the herd (culling) compared to those cows treated only with penethamate.[8] In a European study the use of meloxicam in conjunction with antimicrobial therapy, for mild to moderate cases of clinical mastitis, resulted in a higher probability of bacteriological cure, an increased probability of conception to first artificial insemination, fewer artificial inseminations per pregnancy, and a greater proportion of cows pregnant by 120 days in milk.[9]

It is also important to consider the psychological effects of mastitis. Automated measures of activity, such as step count and lying down time are now being used as predictors of clinical problems and provide potential for early intervention with NSAID therapy.[10] These measurements indicate the administration of an NSAID to cows with mild or moderate clinical mastitis is important for cow wellbeing and pain relief, as well as benefits related to the clinical mastitis, SCC or culling for mastitis.[11]

Mastitis caused by Gram negative bacteria

Coliform / Gram negative bacteria account for approximately 11% of clinical mastitis cases in NZ and 99% of bacteria from these cases have an MIC >4 for common intramammary antibiotics tested.[5]

All NSAIDs have an anti-endotoxic effect. Gram negative endotoxin challenge studies show the administration of ketoprofen or meloxicam reduced rectal temperature and udder oedema, and increased ruminal contractions when compared with control animals.[6]

In a study of high-producing cows with acute clinical mastitis, ketoprofen in addition to antibiotic treatment for up to 5 days significantly increased the chance of cows recovering to >75% of pre-mastitis daily milk production, and these cows were less likely to be culled during that lactation compared to cows that did not receive ketoprofen treatment.[26]

For mild to moderate cases of clinical mastitis caused by *E. coli*, a non-antimicrobial approach with NSAID treatment with frequent milking is recommended. In cases of acute / severe *E. coli* mastitis, parenteral administration of fluoroquinolones, or third- or fourth-generation cephalosporins may be used. However, the evidence for the efficacy of intramammary-administered antimicrobial treatment for *E. coli* mastitis is very limited and hence cannot be recommended.[7]

Pain relief for lame cows

Lameness is painful, negatively impacting cow wellbeing, and can reduce the overall lifetime performance and hence efficiency of dairy cows, due to milk production loss and culling.[12]

Most lameness results from damage to the corium and the subsequent inflammation, often occurring around the time of calving. Weeks to months later, this corium damage may present clinically as claw horn lesions (CHL). In NZ dairy cows, the most commonly identified CHL is white line disease[27] although sole haemorrhage, sole ulcers, and toe abscesses may also be identified. The pain from moderate to severe lameness will cause the cow to limp. For mild lameness the gait and behaviour changes will be more subtle.

Prompt identification and effective treatment of dairy cow lameness is crucial for reducing lameness in the herd. Regular lameness scoring is one of the best ways to identify and manage lame cows earlier.[28] New on-farm technologies may help to improve the prompt identification of lame cows in the future.

Following a clinical case of lameness, there can be permanent bony changes (exostoses) to the pedal bone as a result of the inflammation[25] (Figure 2). These changes are irreversible, and increase the risk of a cow becoming lame again in the future.

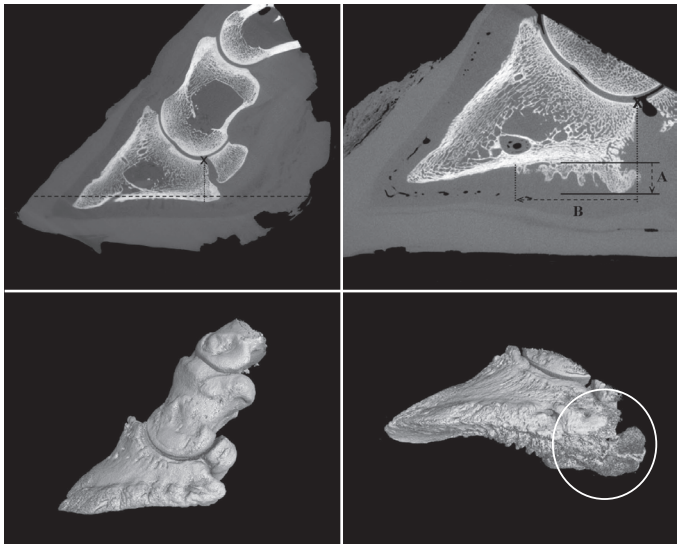


Figure 2. Sagittal x-ray views (top) and 3-dimensional images of normal (left) and diseased (right) bovine digits showing extensive exostosis (in circles) [25]

Effective lameness treatment

Treatment of a lame cow should start with administration of a NSAID to treat the pain and inflammation associated with lameness and the act of treating it. Next, lift the hoof to identify the type of lameness, if a claw horn lesion is present, trim the affected claw and apply a hoof block to the sound claw. Redistributing weight away from the lame claw improves cow comfort, and allows time for the corium to produce new horn tissue. When a bacterial infection such as footrot is identified then antibiotic treatment may be appropriate.

The benefits of ketoprofen

Because lameness is an inflammatory process, NSAIDs are indicated for all cases of lameness, and have been shown to increase the rate of cure. As meloxicam has an 84-hour withholding period for milk, NSAIDs with nil withholding period such as ketoprofen are more popular with dairy farmers.

In a UK study, dairy cows with claw horn lesions that were treated with a therapeutic trim, a block on the sound claw, and a 3-day course of ketoprofen were less likely to be lame five weeks after treatment than a trim alone[14] (Figure 3).

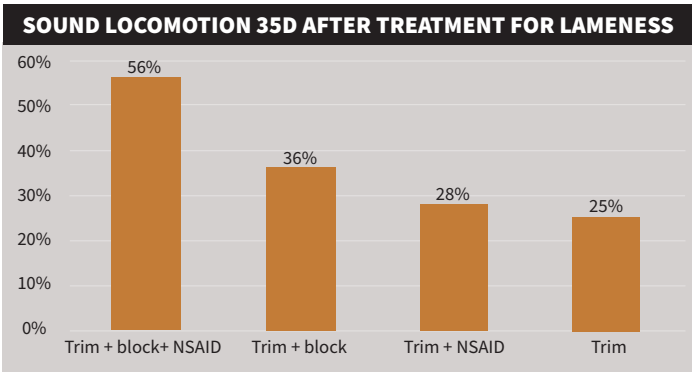


Figure 3. Lameness cure is maximised when ketoprofen is administered along with therapeutic trimming and elevation of the diseased claw using a block[14]

Whilst lame cows gradually recover, they remain at higher risk of recurrent future lameness and earlier culling from the herd. Consequently, it is paramount to reduce the incidence and duration of any lameness.

A recent 3 year longitudinal, randomised, controlled UK Study assessed the role of ketoprofen (sold as KetoMax brand in NZ) in lameness treatment[15] (Figure 4). Treatment Group 1 included routine lameness identification via fortnightly lameness scoring, and a subsequent corrective trim and block for lame animals. Treatment Group 2 and 3 had the same lameness management, and were also treated with 3 days of ketoprofen following identification of each lameness event. Group 3 additionally had ketoprofen for 3 days following their first and subsequent calvings.[15]

	TREATMENT			RESULTS		
	Every calving	When detected as lame		Risk of any lameness	Risk of severe lameness	Risk of culling
	3 days Ketoprofen	Trim + Block	3 days Ketoprofen	odds ratio *(p value)*	odds ratio *(p value)*	hazard ratio *(p value)*
Group 1	✖	✔	✖	Reference	Reference	Reference
Group 2	✖	✔	✔	0.75 *(0.1)*	0.61 *(0.32)*	0.55 *(0.02)**
Group 3	✔	✔	✔	0.66 *(0.03)**	0.28 *(0.04)**	0.56 *(<0.01)***
Group 4	✖	✖	✔	1.04 *(0.83)*	0.74 *(0.57)*	0.75 *(0.25)*

*Figure 4. Three-year study results for heifers treated with ketoprofen when lame and at calving[15] (*P <0.05).*

The study outcomes were very compelling. By the end of the three-year study, twice as many animals in Group 1 were lost from the herd (culled for any reason) during the study, compared with Group 2 and 3. Group 3 cows had a statistically significant reduced risk of lameness when compared to their Group 1 herd mates.[15] Further research is needed to assess the impact of NSAIDs administered at calving. However, several studies now demonstrate the benefits of promptly identifying lame cows and treating them with a trim, block and three days of ketoprofen to improve cure rates and reduce further lameness and culling.

Summary and take-home messages:

NSAIDs reduce both the physiological and psychological effects of pain, so that cows can return to normal function and behaviour, and production, faster.

- NSAIDs are indicated for mastitis, lameness, dystocia and after surgery.
- Ketoprofen and meloxicam are safe to use at all stages of lactation, although meloxicam has a 84 hour withholding period for milk.
- For lameness there is growing evidence that prompt identification and effective treatment, including a trim, block and 3 days of ketoprofen improves cure rates and reduces the risk of further lameness and culling in dairy cows.
- Use of NSAIDs is key to reducing pain and inflammation, resulting in improved health outcomes and hence animal efficiency of dairy cows. In turn this demonstrates better cow care and a more sustainable NZ dairy farming industry helping to meet the expectations of consumers of our dairy products.

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