Role of anti-inflammatory treatments for bovine mastitis

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Mastitis is by definition inflammation of the mammary gland. Mastitis has local effects including changes to the milk (for example presence of flecks or clots or wateriness) and the mammary gland (for example heat, swelling, pain), and in some cases systemic changes including pyrexia and inappetence (Ruegg and Petersson-Wolfe 2018). The mortality rate associated with clinical mastitis in New Zealand is generally low but may occur associated with *Escherichia coli* or *Staphylococcus aureus* infections. Mastitis also has negative effects on reproductive performance, including a longer interval from calving to conception, more services per conception (Barker *et al.* 1998; Schrick *et al.* 2001), lower conception rates (Santos *et al.* 2004; Lavon *et al.* 2011) and a higher risk of embryo loss (Chebel *et al.* 2004; McDougall *et al.* 2005). Cows diagnosed with clinical mastitis are also 1.3 to 1.5 times more likely to be removed prematurely than cows not diagnosed with clinical mastitis (Beaudeau *et al.* 1995; Heuer *et al*. 1999; Santos *et al.* 2004).

As the primary cause of mastitis is generally bacterial, antimicrobials are the standard treatment. However, due to the negative effects of excessive an inflammatory response, anti-inflammatory therapy is indicated. There is a balance between an appropriate pro-inflammatory and pro-resolving host response to limit tissue damage (Aitken *et al.* 2011). With effective antimicrobial therapy, ongoing inflammatory response is unlikely to be required. For this reason anti-inflammatory therapy with either corticosteroids or nonsteroidal anti-inflammatories (NSAID) has long been used for mastitis therapy (Lohuis et al. 1989; Suojala *et al.* 2013; McDougall *et al.* 2016).

The mechanisms of action differ between corticosteroids and NSAID's, and there is variation amongst compounds within class in efficacy and actions. Corticosteroids are hormones released from the adrenal cortex that act via a glucocorticoid receptor (GR) which results in genomic and non-genomic effects. The effect of glucocorticoids varies amongst tissue types due to the presence of multiple isoforms of the GR and post-translational modifications. Corticosteroids have many developmental, homeostatic, metabolic, cognitive and anti-inflammatory effects. Multiple side-effects have ascribed to corticosteroids, particularly with long-term usage, but as mastitis therapy is generally for a relatively short time, there are likely limited side-effects (Ramamoorthy and Cidlowski 2016). The anti-inflammatory effect of corticosteroids is at mediated by leukocytopenia resulting in reduced numbers of neutrophils and monocytes at the site of inflammation, inhibition of monocyte and phagocytic actions (Fauci *et al.* 1976) and inhibition of production of pro-inflammatory cytokines. In ruminants, corticosteroids play a role in mammary gland development, working synergistically with prolactin, and there are GR receptors in the duct and secretory cells but not myoepithelial or mesenchymal cells. However large exogenous doses of corticosteroids may have inhibitory effects on milk yield and reduce milk fat and protein production (Ma *et al.* 2023). Parenteral injection of dexamethasone in cows in negative energy balance resulted in reduced oxidative burst activity and reduced proliferation and possible reduced immune function (Ollier *et al.* 2016). Recent New Zealand data suggests no inhibition of intramammary immune function following intramammary infusion of corticosteroids (Munn and McDougall, unpublished). Conversely intramammary application of corticosteroids may accelerate repair of the blood milk barrier, reduce SCC and inhibit production of pro-inflammatory cytokines (Wall *et al.* 2016).

Non-steroidal anti-inflammatory drugs possess anti-inflammatory, antipyretic, and analgesic properties (Smith, 2003). NSAIDs may be non-selective or selectively inhibit COX-1 or COX-2. Meloxicam is a preferential COX-2 inhibitor while carprofen and ketoprofen are non-selective (van Hecken *et al.* 2000; Lees *et al.* 2004). There are multiple NSAID chemical groups including enolic acids (meloxicam), fenemates (flunixin; tolfedine) and proprionic acids (ketoprofen, carprofen) (Arfeen *et al.* 2024). Products with label claims for mastitis treatment in New Zealand include carprofen, ketoprofen, tolfedine and meloxicam.

Both steroid and NSAID's have been used in severe systemic clinical mastitis cases or in LPS induced mastitis models. Systemic treatment with 30mg of dexamethasone i.m. following intramammary challenge with *E. coli* resulted in reduced milk yield depression, reduced inflammation and diminished inhibition of rumen contraction (Lohuis *et al.* 1989). A narrative review found that steroids do have positive effects, but that treatment needs to occur early in the inflammatory process. Overall NSAID are the preferred option for severe clinical mastitis associated with Gram-negative infections (Suojala *et al.* 2013).

A single systemic treatment with meloxicam, in conjunction with antimicrobial therapy, of mild-to-moderate clinical mastitis cases resulted in lower SCC and reduced risk of culling compared with control cows not treated with an NSAID (McDougall *et al.* 2009). Parenteral treatment with meloxicam also improved bacteriological cure rate following antimicrobial therapy, compared with antimicrobial therapy alone of milk to moderate clinical mastitis cases, predominantly due to Gram-positive bacteria (McDougall *et al*. 2016). In that same study, treatment with meloxicam resulted in a higher proportion of cows conceiving to their first AI (0.31 vs. 0.21) and a higher proportion of cows being pregnant by 120 days after calving (0.40 vs. 0.31). Economic modelling found addition of meloxicam to mastitis treatment regimens was cost-effective across a wide range of dairy production systems for mild-to-moderate mastitis cases (van Soest *et al.* 2018).

Daily parenteral treatment with ketoprofen in conjunction with parenteral trimethoprim/sulphadiazine of acute clinical mastitis cases, predominantly associated with Gram-negative bacteria, resulted in a higher proportion of cows recovering milk yield to 75% of pretreatment levels and a reduced mortality rate compared to cows not treated with ketoprofen (Shpigel *et al.* 1994). Ketoprofen treatment of culture-negative mild cases of clinical mastitis did not improve clinical or bacteriological outcome compared to no treatment (Latosinski *et al.* 2020). Carprofen administered nine hours after experimental challenge with *E. coli* lowered rectal temperature three and six hours post treatment, and resulted in a faster rate of recovery of rumination compared to untreated controls, but had no effect on pro-inflammatory cytokine concentrations, milk yield or SCC (Vangroenweghe *et al.* 2005). There appear to be no randomised controlled studies of use of carprofen or tolfedine as an adjunct therapy for clinical mastitis cases.

There are several registered intramammary therapies that include corticosteroids, but these products were registered many years ago and there are limited data assessing the benefit of corticosteroids in these formulations. In glands infected with *E. coli* and treated with 20mg prednisolone and cephapirin, or with cephapirin alone, inclusion of prednisolone resulted in lower California mastitis test scores and tended to reduce quarter-level SCC relative to antimicrobial treatment alone (Sipka *et al.* 2013). Additionally, the combination of prednisolone and cephapirin resulted in a smaller increase in the pro-inflammatory cytokine interleukin-4, relative to antimicrobial therapy alone, but there was no difference between the prednisolone and cephapirin versus cephapirin alone, for other cytokines including IL-1β, IL-10, and IFN-γ. The small sample size of that study (n = 6 cows) reduced study power (Sipka *et al.* 2014). Hydrocortisone aceponate (HCA) is a synthetic glucocorticoid that has dose-dependent anti-inflammatory and immunosuppressive properties (FDA 2011). Recent New Zealand studies have demonstrated that intramammary infusion of a combination of HCA and penicillin resulted in reduced severity of clinical signs and no depression of bacteriological cure rate, compared to naturally occurring clinical mastitis cases treated with penicillin alone (Munn and McDougall, unpublished data).

In conclusion, anti-inflammatories are important adjunct therapy for bovine mastitis. Benefits are seen both in severe (systemic) as well as mild-to-moderate clinical mastitis cases. Additionally mild to moderate clinical mastitis cases associated with both Gram-positive and Gram-negative bacteria benefit from anti-inflammatory therapy. The benefits of anti-inflammatory treatment include reducing localised inflammation and providing systemic effects such as improved reproduction and increased survival within the herd. Such interventions are cost-effective across a range of production levels, milk payments and treatment costs. Meloxicam administered parenterally has been demonstrated to reduce SCC, improve bacteriological cure rates, and improve subsequent cow fertility when used in conjunction with antimicrobials. Evidence from randomised controlled studies of naturally occurring mastitis cases for use of other NSAID is currently lacking. Inclusion of steroids in intramammary antimicrobial preparations reduces severity of clinical signs.

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