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Brief Communication

Phenylbutazone and Flunixin Meglumine Fail to Show Beneficial Effects on Bovine Subclinical Mastitis

Inflammation is caused by the release of chemical mediators from tissues and migratory cells. These mediators include leucotrienes and prostaglandins (PGs), which are generated from arachidonic acid (*Vane & Botting* 1987). Elevated concentrations of arachidonic acid metabolites have been found in experimental and spontaneous mastitis, which indicates that these substances may have a role in the pathophysiologic process of mastitis (*Anderson et al.* 1985, *Atroshi et al.* 1986).

The inflammatory reaction changes the micro-environment of the invading pathogens. In mastitis, inflammation seems also to be a means for pathogens to gain more nutrients, as bacteria have been found to grow better in mastitic milk and whey, than in normal milk in vitro (*Mattila & Sandholm* 1986). Reducing the inflammatory condition in the udder might make the circumstances less favourable for the bacterial growth and in this way improve the elimination of infection by the host. There are several possibilities for influencing the inflammatory process by pharmacological means. Some non-steroid anti-inflammatory agents (AIA) have been used in mastitis as antipyretic, analgesic and anti-inflammatory supportive treatments. To date, evidence for a positive effect of these types of drugs in bovine mastitis is insufficient.

This study was conducted on subclinical, chronic mastitis on the grounds of the relative stability of the inflammatory status in the mammary gland. Our aim was to investigate if some non-steroid AIA have any effect on the infection or inflammation status, or bacterial growth in vitro in subclinical mastitis.

Eighteen Finnish Ayrshire cows in their mid lactation were monitored for mastitis using conventional bacteriology and somatic cell counting (SCC), N-acetyl-β-D-glucosaminidase (NAGase) activity and trypsin-inhibitory capacity (TIC) as inflammatory markers (*Mattila & Sandholm* 1986). A total of 24 quarters proved to harbour a persistent infection by major mastitic pathogens (staphylococci (n = 13); streptococci (n = 11)) and a stabilised inflammatory reaction.

Bacterial growth in sterile-filtered whey in vitro was followed-up using 1 strain of each of *Escherichia coli* and *Staphylococcus aureus,* derived from clinical cases of mastitis, as test bacteria. The growth studies were made by a turbidometric method as previously described (*Mattila & Sandholm* 1986). Phenylbutazone (Reumuxol, Lääkefarmos, Finland) was administered intravenously at a dose rate of 10 mg/kg twice at an interval of 24 h to 9 cows (14 mastitic quarters); flunixin meglumine (Finadyne, Schering Corporation, USA) at a dose rate of 2.2 mg/kg, to 9 cows (10 mastitic quarters).

Neither of the AIA tested had a significant effect on the infection or inflammatory status in the quarters, as monitored by bacteriological examination, milk NAGase (Fig. 1 and 2), TIC or SCC. When speculating the possible explanations for these results, seve-

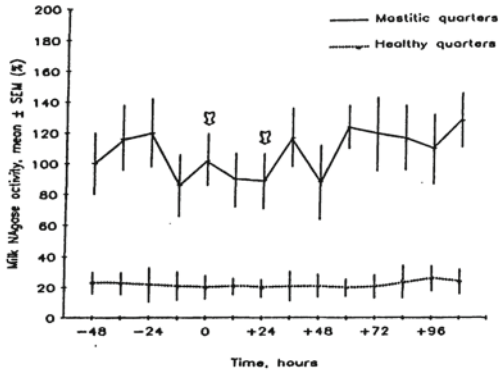

Figure 1. Milk NAGase activity in mastitic and healthy quarters following parenteral infusion of phenylbutazone. NAGase level at the first sampling is marked as 100 %. Infusions of the drug are indicated by an arrow.

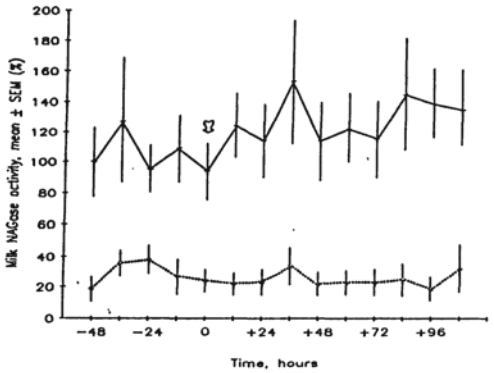

Figure 2. Milk NAGase activity in mastitic and healthy quarters following parenteral infusion of flunixin meglumine. NAGase level at the first sampling is marked as 100 %. Infusion of the drug is indicated by an arrow.

ral potential reasons may be suggested: 1) PGs role in the pathogenesis of chronic, subclinical mastitis is not essential; 2) The parameters measured do not reflect that side of the inflammatory reaction which was affected by the drugs; 3) Subclinical mastitis represents a state of tolerance or suppression of inflammation, where the infection persists but the tissues do not respond as in a normal quarter; 4) Therapeutic concentrations of the AIA used were not reached in the udder. The dosages of both drugs were based on pharmacological data available and are considered sufficient (*Eberhardson et al.* 1979, *Hardee et al.* 1985). According to the pharmacokinetics of phenylbutazone, although the elimination half-life in cattle is longer than in other animal species (more than 30 h), the proportion of the drug leaking into the milk is low (*Martin et al.* 1984). The volume of distribution is small indicating a low degree of tissue uptake of the drug, which is probably due to the high plasma protein binding of the drug.

Repeated dosing of flunixin would have provided some effect, because the calculated elimination half-life is not longer than 8 h. However, it has been demonstrated that clinical response of some non-steroid AIA lasts longer than would be expected on the basis of their half-lives; this long duration of action may be explained by the observation that many of these drugs bind irreversibly to cyclo-oxygenase (*Lees & Higgins* 1985).

In a few quarters, the effect of flunixin was somewhat conflicting, as milk concentrations of inflammation indicators rose slightly after administration of the drug. If this phenomenon was real and not an artifact due to variation in inflamed quarters, one explanation for this finding would be the better supply of arachidonic acid to the lipoxygenase pathway, when cyclo-oxygenase is inhibited by non-steroid AIA. This may lead to more lipoxygenase products being generated (*Sedgwick et al.* 1987). In several trials on acute endotoxin-induced mastitis, a positive effect has been established with flunixin, including antipyretic action and decreased swelling; however, SCC has not been affected (*Anderson et al.* 1986).

One hypothesis for the present study was that suppressing the inflammatory reaction

in the udder, the circumstances would become less favourable for bacterial growth. However, there was no effect on the infection status of the quarters following systemic infusion of the drugs tested, nor on bacterial growth in vitro. The present results of the trial thus failed to support this hypothesis.

The use of anti-inflammatory agents in mastitis is theoretically controversial: they may suppress inflammation and thus reduce tissue damage, but they also interfere with the defence mechanism of the udder. The recently available non-steroid AIA, with fewer side-effects than corticosteroids, are to be considered for inclusion as AIA possibly suitable for mastitis therapy.

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