Nonsteroidal Anti-Inflammatory Drug (NSAID) Administration

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The treatment of dairy cows with nonsteroidal drugs is applied experimentally to investigate the relevance of inflammation during the periparturient period. Despite appearing healthy, dairy cows throughout the transition period and mainly after parturition can develop a pro-inflammatory status that may negatively influence milk production and cows' health. The administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has been demonstrated to have both positive or negative effects on health and milk production, depending on the type of inhibition mechanism, the dose administered and the cows' lactation numbers. At present, the safety and efficacy of NSAIDs have not been irrefutably demonstrated; therefore, their use to improve metabolic and inflammatory status, as well as milk production and cow health after parturition, should be carefully evaluated.

Keywords: NSAID

1. Salicylates

NSAID drugs have been used in the veterinary field since 1875; the first such compound was salicylic acid (SS), a phenolic molecule extracted from willow bark. SS acts by inhibiting COX-1 and -2 activity [1] through transcriptional factor NF-κB inhibition [2]. The plasma half-life of SS in cows is approximately 30 min [3], so a milk withdrawal time of 24 h is considered adequate to avoid residues contaminating the milk [4] (Table 1).

Table 1. Principal qualitative aspects of nonsteroidal anti-inflammatory drugs (NSAIDs).

Drug	Target	Half Time	Milk Withdrawal
Salicylate	**COX-1/2**	**0.5 h**	**24 h**
Flunexin meglumine	**COX-1 preferential**	**1.6 h**	**36–48 h**
Meloxicam	**COX-2 preferential**	**26 h**	**120 h (0.5 mg/kg BW, i.m.) or 80 h (1 mg/kg BW, os)**
Carprofen	**COX-2 selective**	**30.7 h**	**Not required [1]**

[1] in European countries; i.m.: intramuscular; os: oral.

In recent years, an increasing number of studies on transition period dairy cows have investigated the effects of SS administration on health status and milk production. Bertoni et al. [5] conducted the first study that demonstrated milk yield increment and a reduction of plasma acute phase protein levels, e.g., haptoglobin and ceruloplasmin, in multiparous cows treated in the first 5 days of lactation with lysine acetyl salicylate.

Subsequent studies have confirmed the results of Bertoni's study by further explaining how the effects of SS on milk production are influenced by both parity and the basal state of inflammation [6][7][8][9]. Farney et al. [7] enrolled in their study both primiparous and pluriparous cows to which SS (≈123 g/d) was administered in water for 7 days. The SS treatment accelerated the early lactation increase in milk fat secretion, leading to an exacerbated negative energy balance as demonstrate by NEFA and BHBA increment and glucose decrement, according to Bertoni et al. (2004), but not milk yield. In a more detailed study, Farney et al. [8] observed a 21% and 14% increment of milk yield and milk total proteins per lactation in SS-treated, third lactation cows; such a phenomenon had not been described previously [7]. The explanation for this apparent discrepancy, even though experimental conditions were similar, may be the fact that authors in the first study [7] did not classify cows according to parity, thereby likely losing the possibility of observing differences in milk yield, as reported also by Bertoni et al. [5], and increased milk protein yield. Some evidence indicates that multiparity increases

inflammatory pressure [10], so it is possible to hypothesize that SS treatment could promote milk production (see Table 2 for more details on the experimental methods).

Table 2. Summary of studies in periparturient dairy cows reporting doses and timing of treatments with commonly-used nonsteroidal anti-inflammatory drugs (NSAIDs) investigated during the periparturient period of dairy cows.

NSAIDs	N° Total Cows	Dose	Timing [1]	N° Treatment Days	References
Salicylates	78	1.95 g/L (os)	DIM 1 to 7	7	[7]
	78	1.95 g/L (os)	DIM 1 to 7	7	[8]
	51	185 mg/kg (os)	12 to 36 h [2]	3	[6]
	56	125 g/d (os)	12 to 36 h [2]	3	[9]
	22	15 g/d + 7.5 g/d (i.m.)	DIM 1 to 3 + DIM 4 to 5	5	[5]
Flunexin meglumin	26	2.2 mg/kg (i.v.)	within 5 h [2]	3	[11]
	1265	1.1 to 2.2 mg/kg (i.v)	within 24 h [2]	2	[12]
	49	1–5 g in 30 mL (i.m.)	immediately after caesarean	1	[13]
	60	2.2 mg/kg (i.m)	within 12 h [2]	1	[14]
Meloxicam	128	2.2 mg/kg (i.v.)	DIM 5 to 8 [2]	2 bid + 2 sid	[15]
	119	2.2 mg/kg (i.v)	DIM 4 to 5 [2]	1	[16]
	103	0.5 mg/kg (s.c.)	25.4 h [2]	1	[17]
	462	0.5 mg/kg (s.c.)	within 1 h [2]	1	[18]
	60	0.5 mg/kg (s.c.)	within 6 h [2]	1	[19]
	51	~1 mg/kg (os)	12–36 h [2]	4	[6]
	1.009	~1 mg/kg (os)	at calving	1	[20]
	361	0.5 mg/kg (s.c.)	at the diagnosis of c.m.	1	[21]
Carprofen	639	1.4 mg/kg (s.c.)	DIM: 1, 3, 5; DIM 19, 21, 23	3	[22]
	213	1.4 mg/kg (s.c.)	DIM 21 (every 3 days)	3	[23]
	39	1.4 mg/kg (i.v.)	immediately after calving	1	[24]
	60	1.4 mg/kg (s.c.)	within 12 h [2]	1	[14]

[1] start treatment; [2] hours after calving; DIM: Day in Milk; c.m.: clinical mastitis; bid: *bis in die*, twice a day; sid: *semel in die*, once a day; i.m.: intramuscle; i.v.: intravenous: s.c.: subcutaneous; os: oral.

A certain degree of inflammation is necessary to support physiological adaptations in the transition period, but an excess has deleterious effects on milk production. Evidence supporting this hypothesis is provided by the observation of how the presence or absence of an increment in milk yield, milk composition, or milk component yields associated with SS treatment is associated with a different degree of inflammation that cattle experienced at calving, measured as mean haptoglobin concentrations. In one study [9], haptoglobin concentrations were much less than those measured at similar time points in the previous study [6]. Both studies followed the same experimental scheme but the results of milk yield and milk component yields were opposite: in cows with lower haptoglobin concentrations, no differences were observed, whereas in cows with higher haptoglobin concentrations, sustained increases in milk yield were observed in SS cows with respect control cows. A possible adverse effect of the administration of SS is the enhanced risk of the onset of metritis: 30% in SS treated cows compared to 6% of control cows [8]. This data confirms what was previously reported by Bertoni et al. [5]. This increased risk of metritis is likely a consequence of suppressed inflammatory signaling in the immune system. Indeed, the inflammation pathway is essential to activate and attract leukocytes, especially neutrophils, that are critical for the rapid clearance of pathogens [25].

2. Flunixin Meglumine

The N-methyl-d-glucamine salt of flunixin (flunixin meglumine, FM) is a NSAID drug licensed for use in cattle for the modulation of inflammation in endotoxemia and the control of pyrexia associated with tissue trauma, bovine respiratory disease, and acute bovine mastitis [26]. FM works by inhibiting both cyclooxygenase isoforms COX-1 and COX-2, but is more selective for COX-1 [27].

The terminal half-life of this NSAID is from 3.14 to 8.12 h after slow intravenous administration in cattle [28], and the withdrawal time for milk is 36 h [29] (Table 1). Some studies have reported serious side effects following the use of FM on the day of calving due to an increased risk of placental retention (RP) and metritis [12][13]. In particular, Newby et al. [12] published a large-scale study in which cows were randomly assigned to a group undergoing FM treatment and a negative control group. The authors found that cows treated with FM showed a greater chance of having a high temperature, generally associated with mastitis or metritis. Moreover, the authors highlighted that the administration of FM increased the risk of placental retention and stillbirth and reduced milk production (during the first 14 DIM), but did not influence dry matter intake (DMI) [12]. These two side effects seem to be related to antiprostaglandinic effects which may be specific to this NSAID. Indeed, FM preferentially inhibits COX-1 activity, which is mainly responsible for physiological functions, thus explaining the aforementioned undesirable side effects. In another study, Shwartz et al. [11] observed that periparturient cows subjected to FM treatment did not show improvement of milk production during the first 35 days in milk (DIM), and did not differ in milk fat, protein, and lactose when compared to untreated controls. The FM treatment induced an overall reduction in DMI and caused an increase in rectal temperature in the 2 days after calving [11]. Furthermore, FM treated cows show similar concentrations of plasma glucose and NEFA but significantly lower concentrations of serum nitrogen, probably due to reduced DMI in FM-treated cows [11].

Presumably, the contradictory results between the study of Newby et al. [12] and Shwartz et al. [11] could be ascribed to different FM administration schemes (see Table 2) and to different observation windows, up to 35 DIM in the work of Shwartz et al. [11]. A recent study by Giammarco et al. [14] evaluated the effects caused by a single administration of FM (intramuscular) within 12 h after calving on biochemical parameters, DMI, production performance and the fertility of dairy cows. This study, similar to that of Shwartz et al. [11], confirmed that milk yield and composition were not influenced by single dose FM treatment and, more importantly, that the incidence of retained placenta (RP) was drastically reduced with respect control cows, in contrast to what has been reported by other authors [12][11]. Moreover, as also reported by Shwartz et al. [11], DMI was not influenced by FM treatment. In addition, unlike previous studies, the authors did not highlight changes in body temperature. The latter results indicate that the rise in body temperature and increased risk of RP, i.e., side effects of FM, as described in other studies [12][13], could be FM dose related.

In addition, this study revealed significant differences regarding the culling rate in the period preceding 150 DIM in cows treated with FM compared to control cows (15% vs. 25%), suggesting that treatment with FM may be beneficial to periparturient cows when administered in a single dose. In another study, FM administration was associated with the use of combinations of broad-spectrum antibiotics (long-acting oxytetracycline and sulfadoxyne-trimethoprim) for the treatment of animals suffering with puerpueral metritis, causing a significant reduction in pyrexia and a faster clinical improvement followed by a faster uterine involution and a return to estrus [15].

In contrast, in the study of Drillich et al. [16], the association of a single administration of FM with systemic antibiotic treatment (Ceftiofur, a third-generation cephalosporin) in cows with acute puerperal metritis showed no beneficial effect regarding overall health or reproductive performance.

Overall, all of these studies concurred that FM therapy on the day of calving and immediately afterward should not be recommended due to the aforementioned side effects.

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