Commentary

The Potential of Selective COX-2 Inhibitor Mavacoxib for Extended Analgesia in Sheep Husbandry

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Simple Summary:

Routine husbandry procedures like castration, tail docking and mulesing are essential for sheep management and health, but cause significant pain and inflammation lasting up to weeks. Despite this, pain management remains limited, with the most common medication only providing pain relief for up to 48 hours. Mavacoxib is an anti-inflammatory drug currently used in dogs that provides long-lasting pain relief. Its extended action could better match the duration of pain in sheep compared to existing options. Research into mavacoxib for sheep could lead to improved animal welfare and more practical pain management on farms.

Abstract

Routine husbandry procedures in sheep induce significant and prolonged pain and inflammation, which often exceeds the duration of action of current commercially available analgesics. Mavacoxib is a selective cyclooxygenase-2 (COX-2) inhibitor approved for canine osteoarthritis treatment. With a half-life exceeding two weeks, mavacoxib could offer single-dose, extended analgesia, which better aligns with the duration of post-procedural inflammation and pain. This article examines the physiological and behavioural indicators of sheep pain, the limitations of current analgesic strategies, and the pharmacological rationale for mavacoxib as a candidate for pain management in sheep. Further research into its pharmacokinetics, efficacy, and safety in sheep is essential to improve welfare and overcome practical barriers to analgesia in extensive grazing systems.

1. The Painful Reality of Routine Husbandry

With the ever-growing global demand for food and textiles, the sheep industry plays a crucial role in meeting agricultural needs. To improve animal health, productivity, and farm efficiency, routine husbandry procedures, such as ear tagging, castration, tail docking, and mulesing, are regularly performed. Ear tagging facilitates rapid individual identification and improves farm management [1]; castration is used to control breeding and prevent aggressive behaviours [2]; tail docking prevents faecal soiling, thereby reducing the subsequent risk of flystrike [3]; and mulesing, the removal of wool-bearing

skin around the breech, is also aimed at preventing flystrike [4]. While these procedures serve important practical purposes necessary for health and productivity, they cause significant pain and inflammation due to surgical or ischaemic soft tissue damage [5,6], raising serious animal welfare concerns [7].

Despite a growing scientific consensus that these procedures cause considerable pain, they are often performed with inadequate pain management, if any at all. A survey by the Sheep Sustainability Framework [8] found that a substantial proportion of Australian farmers still do not use adequate analgesia during husbandry procedures. As societal expectations for animal welfare continue to evolve, husbandry procedures not only become ethically fraught without adequate analgesic and anti-inflammatory relief, but also biologically counterproductive. Unmanaged pain can suppress immune function, reduce feed intake, impair wound healing, and cause behavioural changes that disrupt flock cohesion and reduce productivity [6].

Currently, only six analgesic and anti-inflammatory drugs are registered for use in sheep in Australia [9]. Drug restrictions further limit accessibility to on-farm use by producers, with three of these needing to be administered by a veterinarian [9]. Additionally, the duration of post-procedural pain and inflammation often exceeds the duration of action of these drugs [10], with pain and inflammation lasting up to weeks [11]. This discrepancy highlights the urgent need for a long-acting nonsteroidal anti-inflammatory drug (NSAID) whose pharmacological duration aligns with the biological course of inflammation. Addressing this need could significantly improve both animal welfare and on-farm productivity.

2. Inflammation and Its Consequences

2.1. Mechanisms of Inflammation

Acute inflammation is the body's immediate response to tissue injury or infection, characterised by redness, heat, swelling, pain, and a loss of function at a tissue level [12]. Although associated with discomfort, inflammation is a protective process that promotes tissue repair by recruiting immune mediators such as cytokines, proteins and chemokines, which attract neutrophils and macrophages to the affected site [12]. The formation and release of pro-inflammatory mediators increase blood flow and fluid accumulation at the site, causing swelling and redness, and sensitise nerve endings, resulting in pain perception [13]. Pain acts as a protective mechanism by discouraging movement and further injury [14], thereby aiding in healing and recovery [15,16].

Among these inflammatory mediators, prostaglandins are of notable importance for their crucial role in regulating various bodily functions, including but not limited to inflammation and pain [17]. They are synthesised from arachidonic acid via cyclooxygenase (COX) enzymes (Figure 1), and contribute to nociceptor activation and peripheral sensitisation [18]. Of the two main COX isoforms, COX-2 is particularly relevant to husbandry procedures, as it is induced during injury and is a key driver of inflammatory pain [19].
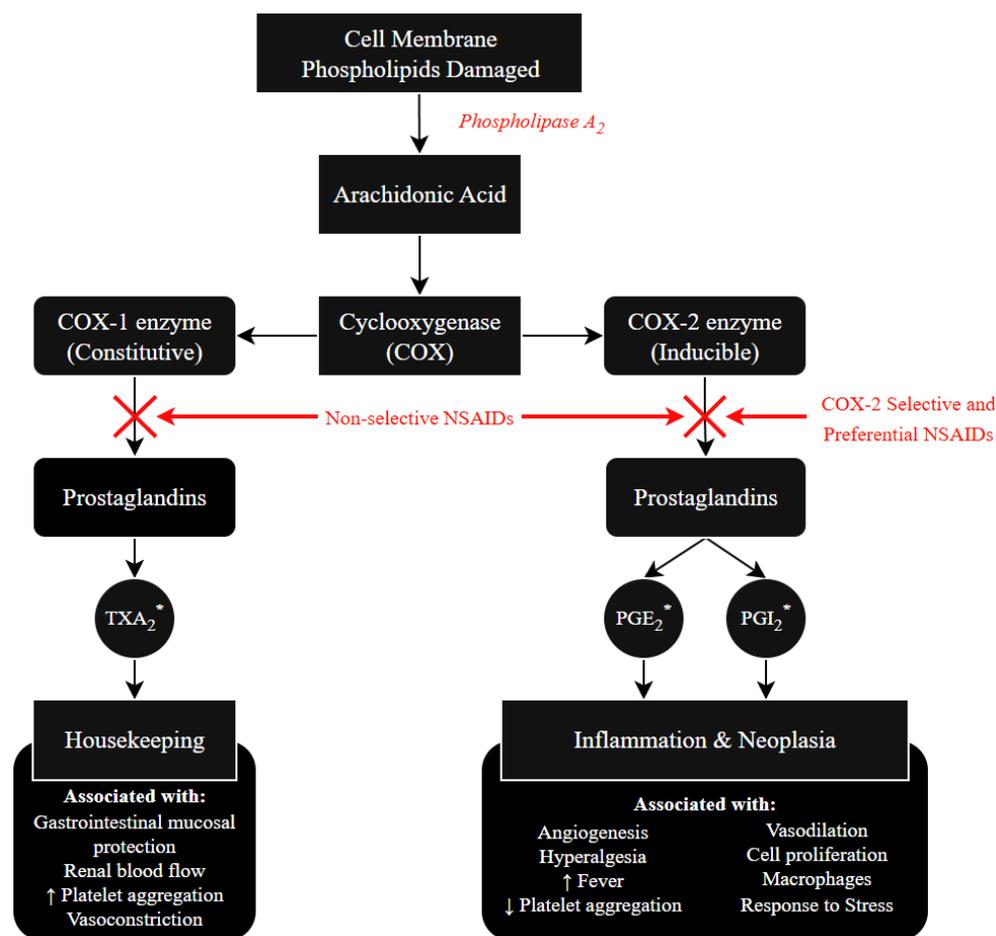
Figure 1. The arachidonic cascade into cyclooxygenase (COX) enzymes, COX-1 and cyclooxygenase-2 (COX-2), and their production of prostaglandins and the respective roles of their derivatives. TXA2 = Thromboxane A2; PGE2 = Prostaglandin E2; PGI2 = Prostaglandin I2; * = prostanoid more significantly produced by the respective COX enzyme it falls under. Adapted from Flood & Stewart [20], and Anwar et al. [21].

2.2. Signs of Inflammatory Pain in Sheep

Pain-related behaviours following husbandry procedures are well documented in sheep [6]. However, accurate assessment is challenging because sheep, as prey animals, instinctively mask signs of weakness or distress [22]. Pain expression in sheep is highly variable and influenced by individual and contextual factors, meaning identical painful stimuli can elicit different responses across animals. Age and sex affect pain sensitivity and behavioural expression, with older lambs displaying higher frequencies of some pain-related behaviours than younger lambs, and male and female lambs diverging in sensitivity during development [23]; notably, female lambs may exhibit more acute pain behaviours than males following tail docking [24]. Behavioural responses are further shaped by personality, prior experience, and social context; for example, the presence of familiar or related conspecifics can attenuate the expression of pain behaviours through social buffering, complicating interpretation in production settings [25].

Pain in sheep can be assessed using both physiological and behavioural indicators. Physiological markers such as elevated plasma cortisol, increased heart rate, and altered respiratory rate are commonly observed following painful interventions [26], but these responses lack specificity as they are also influenced by handling stress, environmental conditions, and social factors [22,26]. While often acute, physiological responses may remain elevated for extended periods following procedures such as mulesing and

castration, indicating prolonged pain states [26]. Behavioural indicators include abnormal postures (e.g., hunched stance or lowered head), reduced activity, altered gait, bruxism, diminished grazing, increased vocalisation, and social withdrawal [22]. Facial expression–based measures, such as pain-specific grimace scales, provide an additional tool for detecting subtle changes in pain-related demeanour, although their application is currently more feasible in controlled environments than in field conditions [6].

Collectively, this demonstrates that pain in sheep is complex, variable and context-dependent, reinforcing the need for controlled approaches and validated experimental models to reliably and systematically study pain mechanisms and analgesic efficacy under reproducible conditions.

2.3. Induced Inflammation Model

Variability in pain indicators has led to the development of an induced inflammation model to provide a controlled and objective method for assessing pain and NSAID efficacy [27]. This model standardises inflammation severity through a subcutaneous injection of 0.1 mL of oil of turpentine into the forelimb pastern of sheep, producing a localised and reproducible inflammatory response lasting approximately 72 hours [27]. This approach eliminates the need for husbandry procedures to induce pain, improving consistency and repeatability, and has been successfully used to evaluate the effects of meloxicam. Studies have reported significant reductions in both behavioural and physiological indicators of inflammation [28,29]. The model was less effective at distinguishing the efficacy of flunixin, carprofen, and ketoprofen, likely due to model limitations and potential suboptimal timing of NSAID administrations [30].

The inflammation model incorporates objective measures that correspond to the five cardinal signs of inflammation: redness, heat, swelling, pain, and loss of function. These indicators enable researchers to track the progression of inflammation and evaluate analgesic efficacy with greater accuracy in sheep. While observing redness is not feasible due to their wool covering, heat at the inflammatory site, caused by vasodilation and an influx of inflammatory mediators [13], can be measured using infrared thermometers, although skin temperature readings may be influenced by ambient temperature and do not reflect core body temperature [27]. Swelling results from increased vascular permeability [13] and can be quantified by limb circumference measurements [27]. Pain, arising from nociceptor activation [18], can be assessed using pressure algometry [27]. Loss of function, driven by pain and swelling, can be evaluated through ordinal gait scoring or weight-bearing assessment using strike plates [27]. Studies using this model show that turpentine injection increases pressure sensitivity by 52% and lameness by 58% [28], lasting up to 12 hours post-administration [29] and reduced weight bearing [27,28], alongside elevated skin temperature and limb circumference [27-30].

The turpentine-induced inflammation model offers strong experimental control and reproducibility but does not fully capture the complexity of clinical pain experienced by livestock following surgical husbandry procedures. Field pain is intricate, arising from ongoing tissue damage, inflammation, nerve injury, central sensitisation, and neuroimmune interactions, with physiological and environmental stressors further contributing to its chronic and prolonged nature [31,32]. These components extend beyond the acute inflammatory response modelled by turpentine injection and are therefore not fully represented in controlled laboratory settings.

As a result, findings from induced inflammation models may not directly translate to on-farm conditions, where animals experience prolonged pain while exposed to environmental stressors, variable nutrition and hydration, and increased risks of infection and further injury [33]. Recognising these limitations is essential when interpreting

experimental outcomes and underscores the importance of complementary field-based validation to establish the clinical relevance of laboratory findings.

Together, these indicators provide a comprehensive, quantifiable, and relatively underutilised foundation for assessing pain and the effectiveness of analgesics in sheep. The capacity of the model to integrate multiple dimensions of inflammation makes it a valuable tool for future research in veterinary pain management and animal welfare.

3. NSAIDs and Analgesics in Livestock Practice

3.1. What Is Currently Used?

Currently, only six analgesic products are registered for ovine use in Australia, reflecting a limited pharmacological toolkit for pain management in this species [9]. These include injectable lignocaine as a local anaesthetic; ketamine and xylazine for sedation and anaesthesia; Tri-Solfen® (Dechra Veterinary Products Australia, Somersby, New South Wales), a topical anaesthetic (contains lignocaine, bupivacaine, adrenaline, and cetrimide); and meloxicam, which is available in both oral transmucosal and injectable forms and is currently the only NSAID registered for use in sheep in Australia [9].

This limited availability poses a challenge for effective pain relief in sheep during routine husbandry procedures. Inadequate pain management not only compromises animal welfare but also has broader implications, including prolonged cortisol elevation, which can suppress immune function and reduce feed intake and weight gain [34]. These effects ultimately reduce productivity and increase economic losses, further highlighting the importance of accessible and effective pain mitigation strategies in livestock [6].

3.1. The State of Current Analgesic Options

A single dose of currently available analgesics provides only short-term relief, far shorter than the duration of pain following procedures such as castration or tail docking [11]. For example, meloxicam's analgesic effects persist for up to 48 hours in sheep [28,29], whereas pain and inflammation can persist for 3 to 90 days [11]. In contrast, companion animals undergoing comparable surgical interventions frequently receive multiple doses of analgesics; for instance, dogs are routinely administered oral meloxicam daily for 3-5 days following surgery [35]. To maintain analgesic therapeutic levels that better match the window of inflammation and pain, repeated dosing would be needed, but impractical due to concerns about drug residues [36] and the logistical challenges of rehandling animals in extensive grazing systems [37]. These barriers highlight the need for long-acting analgesics that provide extended pain relief with minimal intervention.

Despite the availability of approved analgesics, producer uptake of pain relief remains low, particularly in extensive sheep production systems. Surveys from the Sheep Sustainability Framework [8] report that 75% of producers do not use pain management for castration, and 56% do not for tail docking. Contributing factors include the logistical burden of repeat administration and the perceived lack of justification for analgesia [8]. Continued reliance on short-acting drugs, whose analgesic effects diminish before inflammation subsides [10,11], further highlights a critical gap in pain management and the urgent need for innovative, long-acting, single-dose analgesics that align with the biological reality of post-procedural pain in sheep.

4. Mavacoxib: A Promising Long-Acting Analgesic?

4.1. Pharmacological Rationale and Safety Considerations for Use in Sheep

Mavacoxib is a highly selective COX-2 inhibitor from the COXIB class of NSAIDs, and is currently approved only for canine osteoarthritis and has been studied in dogs [38],

rabbits [39], and some avian species [40–43]. Its efficacy, safety, and optimal dosing regimens in sheep remain unknown. Unlike non-selective NSAIDs, COXIBs exhibit greater specificity for COX-2 inhibition over COX-1 [44]. The COX-1 isoform is a "housekeeping" enzyme, constitutively expressed in most tissues, where it produces prostaglandins maintaining homeostatic processes such as gastrointestinal integrity, renal function, blood clotting, and hormone regulation [19,45]. In contrast, COX-2 is primarily upregulated during inflammation and tissue injury, driving prostaglandin synthesis and contributing to pain, swelling, and fever [44,46]. However, COX-2 is not exclusively an inducible enzyme; it is also constitutively expressed in certain tissues, including the kidneys, where it regulates renal haemodynamics and homeostasis [47], and reproductive tissues, where it plays roles in fertility and gestation [48]. Therefore, while COX-2 inhibitors such as mavacoxib minimise COX-1-associated adverse effects, they may still affect normal physiological functions [49]. Although both enzymes produce prostaglandins, they play functionally distinct roles, with COX-1 maintaining physiological balance and COX-2 mediating inflammation and pain.

In-vitro assays using canine blood demonstrate that mavacoxib is between 37.8- to 128-fold more selective for COX-2 than COX-1 [50,51], compared to meloxicam, which is only 12-fold more selective [52]. This profile is desirable for pain management in livestock, as it targets the inflammatory pathways directly while minimising off-target effects associated with COX-1 inhibition, such as gastrointestinal ulceration and renal dysfunction [21,53,54].

While efficacy is critical, NSAID use also depends on safety, as prostaglandin inhibition underlies both therapeutic and adverse effects. Adverse reactions most commonly affect the gastrointestinal tract, kidneys, and liver [55], with gastrointestinal lesions presenting as irritation, erosion, or ulceration, potentially causing anaemia, protein-losing enteropathy, or melaena [56,57]. In dogs, mavacoxib (Trocoxil 20 mg chewable tablets for dogs) most frequently reported adverse reactions are vomiting and diarrhoea, with uncommon reports of appetite loss, haemorrhagic diarrhoea and melaena, and rarely observed gastrointestinal ulceration [58]. Although COX-2–selective NSAIDs can induce ulceration in monogastrics [53,58], there is no evidence of NSAID-induced abomasitis or intestinal perforation in ruminants [10,59]; notably, one study reported cattle given meloxicam 30 times (30 mg/kg) the recommended dose (1 mg/kg) showed no adverse effects or gross histologic lesions [57]. While the long half-life of mavacoxib raises considerations regarding tissue persistence and withdrawal periods [36], its favourable pharmacodynamic profile suggests strong potential for safe, effective, welfare-aligned analgesia in sheep, pending further investigation for commercial application.

4.2. The Pharmacokinetics of Mavacoxib

Pharmacokinetic data from dogs show that mavacoxib demonstrates a remarkably low clearance rate of 0.0027 L/hr/kg, ~130-fold lower than the low clearance rate threshold for dogs of the same weight (0.348 L/hr/kg) [60], and a prolonged half-life of 17.3 days [38]. Its lipophilicity further suggests extensive distribution into inflamed tissues, offering targeted analgesia at wound sites [44], a favourable characteristic for procedures like castration and tail docking. The low clearance rate and minimal renal excretion, with elimination predominantly via biliary secretion and faecal excretion [44], distinguish mavacoxib from NSAIDs such as meloxicam and carprofen, which rely on renal and faecal pathways [61-63]. This also means accumulation may occur in animals with hepatic impairment, explaining its contraindication in dogs with liver disease [64]. Its long half-life is further supported by high plasma protein binding, large volume of distribution, and enterohepatic recycling [65]. While sheep may have faster metabolism and different bile flow that could shorten the half-life [66,67] hepatic metabolism and biliary elimination are

likely conserved, allowing slow excretion and extended therapeutic exposure [66] 250
although direct extrapolation from dogs to sheep requires evaluation, existing 251
pharmacokinetics and knowledge of NSAID behaviour in both species [61] suggest multi- 252
day or week-long analgesia may be achievable with a single dose. 253

4.3. Addressing The Inflammation Duration Mismatch in Current Analgesics 254

The extended duration of action provided by mavacoxib offers significant welfare 255
advantages by aligning analgesia with the extended inflammatory response associated 256
with husbandry practices, which often span several days to weeks [10]. This contrasts with 257
meloxicam, which possesses a much shorter half-life and significantly higher clearance 258
rate (Table 1) and requires frequent redosing to sustain therapeutic efficacy [61]. Improved 259
alignment between pharmacokinetics and inflammatory windows may promote greater 260
compliance with pain relief protocols, improve animal welfare, and potentially enhance 261
growth performance and productivity outcomes [6]. Collectively, these features highlight 262
the strong potential of mavacoxib for integration into livestock pain management 263
strategies, warranting further investigation. 264

Table 1. Comparison of pharmacokinetic data of single-dose meloxicam for sheep and dogs. 265

Study	Species	Dose/Route	C_{max} (µg/mL)	T_{max} (hours)	$t_{1/2}$ (days)	$AUC_{0-\infty}$ (µg/mL*h)	Cl (L/hr/kg)
Woodland et al. [29]	Sheep	1 mg/kg SC	6.96 ± 1.03	4.67 ± 1.03	10.82 ± 2.46	129.89 ± 27.54	0.008 ± 0.002
Boehringer Ingelheim Animal Health USA Inc [68]	Dog	0.2 mg/kg SC	0.734	2.5	24 (approx.)	-	0.01

Route = route of administration; C_{max} = maximum plasma concentration; T_{max} = time to reach 266
maximum plasma concentration; $t_{1/2}$ = elimination half-life; $AUC_{0-\infty}$ = area under the plasma 267
concentration-time curve from time 0 to infinity; Cl = clearance; SC = subcutaneous. 268

5. Conclusions 269

The extended pharmacokinetic profile of mavacoxib offers significant potential to 270
address current limitations in sheep analgesia. With growing welfare concerns around 271
routine husbandry, long-acting and practical pain relief is urgently needed. The 272
prolonged half-life and selective COX-2 inhibition of mavacoxib suggest it could offer 273
sustained multi-day or even week-long analgesia. 274

To realise this potential, further pharmacokinetic and efficacy studies in sheep are 275
essential, ideally employing standardised inflammation models, to clarify its therapeutic 276
potential and optimal dosing regimens for use in sheep. Key outstanding questions 277
remain, including: What are the specific pharmacokinetic parameters of mavacoxib in 278
sheep following various routes of administration? What is the optimal single dose 279
required to achieve effective and sustained analgesia in routine husbandry procedures? 280
How long do its analgesic and anti-inflammatory effects persist under extensive grazing 281
conditions compared to existing agents such as meloxicam? And finally, are there notable 282
species-specific differences in metabolism or potential adverse effects between canine and 283
ovine physiology that warrant careful consideration? 284

Importantly, the single-dose administration potential of mavacoxib could reduce the 285
stress and labour associated with repeated handling, a major barrier in large-scale 286
operations. This would improve compliance with animal welfare guidelines and 287
encourage broader adoption of humane, sustainable livestock management. If validated, 288
mavacoxib could become a valuable tool not only in sheep but also across the wider 289
livestock industry, shaping future pain management strategies. Its practical benefits 290

warrant serious consideration for continued research into its safe and effective application.

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Abbreviations

The following abbreviations are used in this manuscript:

NSAID	Nonsteroidal anti-inflammatory drug
COX	Cyclooxygenase

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