Current Trends and New Developments in Assessing and Managing Pain in Cattle

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Abstract

Pain management in cattle presents unique challenges due to regulatory considerations, cost, and difficulty assessing pain in these animals. This presentation summarizes key findings from recent research on pain management practices in the beef and dairy industry, focusing on the use of analgesics, challenges in drug approval, and the communication and perspectives between producers and veterinarians.The research highlights the increased use of pain management in older cattle, with veterinarians showing greater odds of utilizing analgesia compared to producers. Painful routine procedures, such as castration and dehorning, are identified as common sources of pain for cattle, emphasizing the need for effective pain mitigation strategies. However, the limited availability of FDA-approved drugs for pain management in cattle poses significant challenges for industry stakeholders, both financially and practically.Furthermore, this presentation explores communication and perspectives regarding pain management between producers and veterinarians, aiming to understand the impact of disagreements on their relationship and their perceptions of recognizing pain in cattle. The findings underscore the necessity for more FDA-approved pain management drugs for use in cattle to address the challenges the beef and dairy industry faces.

Challenges Associated with Providing Analgesia in Food Animals

Several challenges exist with providing adequate analgesia in food animals in the U.S. Firstly, no analgesic drugs are specifically approved for alleviating pain associated with dehorning and castration in livestock. Therefore, the use of any drug for pain relief constitutes extra-label drug use (ELDU). Under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA),ELDU is permitted to relieve suffering in cattle provided specific conditions are met. These conditions include that (1) ELDU is allowed only by or under the supervision of a veterinarian, (2) ELDU is allowed only for FDA-approved animal and human drugs; (3) ELDU is only permitted when the health of the animal is threatened and not for production purposes; (4) ELDU in feed is prohibited and (5) ELDU is not permitted if it results in a violative drug residue in food intended for human consumption. Therefore, the use of an analgesic to alleviate pain associated with castration in calves in the US would be required by law to comply with these regulations (Coetzee, 2013).

A second challenge to providing effective analgesia in cattle is that there is often a delay between the time of drug administration and the onset of analgesic activity. For example, local anesthetics require 2 to 5 minutes (min) before a maximal effect is achieved. This may slow animal processing as producers must wait for local anesthesia to take effect. This delay may be a disincentive for them to provide routine preemptive analgesia. Furthermore, the requirement for large numbers of animals to be processed quickly may result in procedures being initiated before optimal analgesia is achieved. A third challenge is that the route or method of analgesic drug administration may require specialized training and expertise or may be hazardous to the operator. For example, generic injectable formulations of flunixin meglumine are only approved for IV administration in the US. Therefore, administration requires the animal to be adequately

restrained and the operator to be proficient in IV administration, highlighting the potential risks. Similar issues are encountered with epidural analgesic drug administration and administration of local anesthesia into the scrotum. The latter procedure is also considered especially hazardous by many livestock handlers. In addition, the majority of analgesic drugs that are available in the U.S. have a short elimination half-life, necessitating frequent administration to be effective. This increases the individual animal's stress and labor and drug costs.

In addition to the regulatory considerations discussed previously, certain drug classes, such as the opioid and NMDA receptor antagonists, are designated as Schedule 3 drugs and are subject to regulation by the U.S. Drug Enforcement Administration (DEA). Therefore, the administration of these compounds to provide pre-emptive analgesia is restricted to use by licensed veterinarians. Finally, the cost associated with providing preemptive analgesia contributes to the reluctance of producers to adopt these measures, especially since there is no perceived economic benefit to doing so. It may also be problematic for producers and veterinarians to determine if analgesic compounds are effective because cattle may not show overt signs of pain and distress; thus, determining the need for analgesia and the dose, route, duration, and frequency of drug administration in cattle can be especially challenging.

Current trends in managing pain in cattle

A recent collaborative survey published by our research group in the Journal of the American Veterinary Medical Association aimed to evaluate the current pain management practices and opinions of veterinarians and producers within the beef and dairy industry in the United States (Johnstone et al., 2021). The survey included 1,187 respondents from various organizations, and the data was collected from May to August 2018. The results indicated that the use of analgesics

increased with the age of the cattle, with 57.6% of respondents using pain management in calves under two months old and 71.6% using pain management in adult cattle over 12 months old. Notably, veterinarians were found to have significantly greater odds of using analgesia than producers in all age categories of cattle.The research emphasized the importance of recognizing and treating cattle pain to minimize animal suffering, optimize animal health and well-being, and maximize production and profit. Painful routine management practices, such as castration, disbudding, dehorning, lameness, and mastitis, were identified as common sources of pain for cattle. The study highlighted that pharmaceutical interventions for pain mitigation in cattle primarily consist of local anesthetics and systemic analgesics. However, challenges were noted, including the lack of FDA-approved drugs for pain management in cattle intended for food production. Notably, flunixin meglumine is the only NSAID approved in the US for the treatment of pain in cattle, and it is limited to specific conditions. The authors also noted that in the United Kingdom, several NSAIDs are approved for use in cattle, which contrasts with the limited options available in the US. The lack of approved drugs for pain management in cattle presents significant challenges for ranchers, farmers, and veterinarians, both from financial and practical perspectives. Consequently, there is a need for more FDA-approved pain management drugs for use in cattle to address the challenges faced by those involved in the beef and dairy industry.

A second survey published in collaboration with Colorado State University explored the communication and perspectives regarding pain management in cattle between producers and veterinarians (Mijares et al.,2023). The research aims to understand how disagreements about pain mitigation may affect their relationship and to determine their perceptions of recognizing

pain in cattle. The survey, distributed to dairy and beef cattle industry groups, received over 1,000 responses from producers and veterinarians. Most producers believed that disagreements about pain management never affected their relationship with their veterinarians. Veterinarians indicated more frequent disagreements, but the majority were still infrequent. Both groups expressed that they were unlikely to dissolve the relationship entirely due to disagreements about pain management. Most producers and veterinarians considered themselves adequately capable of recognizing pain, and they reported gaining their knowledge from various sources such as personal experience, continuing education opportunities, veterinarians, and journal articles. The study suggests an opportunity for veterinarians to engage in more discussions about pain management with producers. The importance of pain management in the cattle industry is highlighted by various guidelines and programs that recommend or require pain mitigation during procedures such as dehorning and disbudding. Despite the increasing expectations regarding the routine use of analgesia, little is known about the discussions between producers and veterinarians on this topic. Therefore, understanding their perspectives and improving communication is crucial for developing and implementing effective pain management protocols for cattle. In conclusion, the study provides insight into the communication dynamics between producers and veterinarians regarding pain management in cattle. It suggests the need for more extensive discussions and educational programs to enhance their decision-making processes related to pain mitigation.

A third study published in collaboration with North Carolina State University analyzed data from the Food Animal Residue Avoidance Databank (FARAD) regarding inquiries received about analgesic use in cattle (Robles et al., 2021).The inquiries received by veterinarians through the

FARAD program sought information on drug withdrawal, dosage, route, and contact details. The FARAD results showed that most inquiries from 2015 to 2019 pertained to using flunixin/flunixin meglumine, meloxicam, and acetylsalicylic acid (aspirin) in cattle. The data highlighted the interest and need for guidance on the use of analgesic drugs in cattle and emphasized the role of FARAD in providing scientifically based withdrawal interval recommendations for extra-label drug use in food animals.

New Developments in determining the effectiveness of Pain Assessment Strategies

A recent study by Martin and others examined the diagnostic sensitivity and specificity of pain biomarkers in cattle using receiver operating characteristic (ROC) curves (Martin et al., 2022). The analysis included biomarkers such as plasma cortisol, salivary cortisol, hair cortisol, infrared thermography (IRT), mechanical nociceptive threshold (MNT), substance P, kinematic gait analysis, and a visual analog scale for pain. The retrospective analysis involved a total sample size of 7,992 biomarker outcomes collected from seven pain studies focused on castration, dehorning, lameness, and abdominal surgery.

The results of the ROC analysis indicated that several biomarkers exhibited good diagnostic accuracy, with area under the curve (AUC) values greater than 0.7, particularly when comparing analgesic effects to pain. Specifically, plasma cortisol at various time points (1.5, 2, 3, 4, 6, and 8 hours), hair cortisol at 62 days, and IRT at 72 hours consistently showed good diagnostic accuracy. Additionally, specific time points yielded the best diagnostic accuracy for certain biomarkers. For instance, plasma cortisol at 2 hours following castration and dehorning, IRT at 12 hours following castration, plasma cortisol at 24 hours following lameness induction, and IRT

at 48 hours following dehorning exhibited AUC values greater than 0.75 when comparing analgesia versus pain.Furthermore, specific time points also demonstrated good diagnostic accuracy when comparing pain versus no pain. For example, plasma cortisol at 1 hour following castration and dehorning, IRT at 8 hours following castration, VAS at 24 hours following castration, and plasma cortisol and substance P at 24 hours following lameness induction all exhibited AUC values greater than 0.75.In summary, the study's results suggest that ROC analysis can serve as a valuable indicator of the predictive value of pain biomarkers. Specific time points yield good diagnostic accuracy for particular biomarkers, highlighting their potential in assessing pain and analgesic efficacy in cattle.

New Developments in Managing Pain

Local Anesthesia

Local anesthetics are the most commonly prescribed pre-emptive analgesic drugs used in food-animal practice. These compounds produce reversible loss of sensation in a localized area without causing loss of consciousness. Local anesthetics enter and block open nerve cell sodium channels, preventing generating and propagating nerve impulses.Repeatedly stimulated nerve cells are, therefore, more susceptible to the effects of local anesthetics. Furthermore, local anesthetics preferentially block unmyelinated nerve fibers that transmit pain signals than myelinated fibers responsible for pressure sensation and motor activity. The quality of local anesthesia in an acidic environment, such as infected tissues, is often poor because these compounds are weak bases that must dissociate in an alkaline environment to exert their effect. Lidocaine has a relatively rapid onset of activity (2 to 5 min) and an intermediate duration of action (90 min). Local anesthetic administration into the epidural space has also been shown to

provide regional analgesia of the perineal region commencing 5 min after administration of 0.2 mg/kg lidocaine and lasting 10 to 115 min.

Compounds that potentiate local anesthesia

Magnesium Sulfate (MgSO4) – Magnesium sulfate has been combined with lidocaine to potentiate the local anesthetic effects. Magnesium competitively antagonizes NMDA receptors and their associated ion channels in the same manner as ketamine, thus reducing central sensitization caused by peripheral nociceptive stimulation.It has been reported that the combination of lidocaine with magnesium sulfate produced epidural analgesia of longer duration than lidocaine with distilled water. In this experiment, local anesthesia with 2% lidocaine solution administered at 0.22 mg/kg was potentiated with 1 mL of 10% magnesium sulfate solution. Magnesium also reportedly has antinociceptive effects in animals and humans after systemic administration. These effects are associated with the inhibition of calcium influx into the cell and antagonism of NMDA receptors. Further studies concerning the safety and efficacy of magnesium augmentation of local anesthesia are needed before this technique can be recommended.

Sodium Bicarbonate – Commercial preparations of lidocaine are prepared as acidic solutions to promote solubility and stability. The addition of sodium bicarbonate before administration significantly reduces pain produced by infiltration of lidocaine in humans, probably due to the reduced acidity of the commercial formulation. The addition of sodium bicarbonate to lidocaine has also been found to reduce the time taken for the nerve block to take effect and enhance analgesia in humans. However, the addition of bicarbonate may decrease the duration of the

block. A 10-1 ratio of 2% lidocaine with 8.4% sodium bicarbonate is recommended for optimal buffering of lidocaine. Thus, 1 ml of commercially available 8.4% sodium bicarbonate solution can be added to 10 ml of 2% lidocaine immediately before administration to buffer the acidic effects of the formulation.

Alternatives to Local Anesthesia

Ethanol injection demyelinates nerve fibers and may be a promising long-acting local anesthetic for use during disbudding (Tapper et al., 2011; Martin et al., 2022). When ethanol was administered as a corneal nerve block before disbudding, calves failed to display increased pain sensitivity in response to pressure algometry relative to their baseline values. Furthermore, ethanol-treated calves differed significantly from calves treated with the local anesthetic lidocaine at 1 hour post-disbudding, when the lidocaine was assumed to be wearing off. When the experiment concluded, ethanol blocks appeared to desensitize the site of cautery dehorning for more than 83 hours (h). In this experiment, 2 ml of 100% ethanol was injected at the site of the corneal nerve block. However, more than half the calves subjected to ethanol anesthesia required a second injection to achieve complete loss of sensation in one or both horns. Further studies concerning the safety and efficacy of ethanol blocks for local anesthesia are needed before this technique can be recommended.

Non-steroidal anti-inflammatory Drugs (NSAIDs)

NSAIDs produce analgesia and anti-inflammatory effects by reducing prostaglandin (PG) synthesis through inhibition of the enzyme cyclo-oxygenase (COX) in the peripheral tissues and central nervous system. COX exists in two isoforms. COX-1 is constitutively expressed in both

peripheral and central nervous systems, although pain and inflammatory mediators enhance expression. COX-2 is ubiquitous in the CNS but only becomes the primary enzyme for PG synthesis after induction by factors released during cell damage and death. It takes 2 to 8 hours for maximal COX-2 mRNA expression to occur in the peripheral tissues; therefore,the initial release of PG is primarily due to COX-1. PG in the peripheral tissues lowers the activation threshold of sensory neurons and may initiate nociceptive activity. PG also works with substance P, histamine, calcitonin gene-related peptide (CGRP), and bradykinin to lower the firing threshold of sensory nerves and produce inflammation. Therefore, NSAIDs that inhibit COX-1 may have a more immediate impact on pain by inhibiting PG production in the periphery than COX-2 selective compounds. However, NSAIDs that inhibit COX-1 may be associated with an increased risk for adverse gastrointestinal and renal effects.

Spinal PG, notably PGE_2, is responsible for increased excitability of the dorsal root ganglia, leading to centrally mediated hyperalgesia. Given that COX-2 is constitutively expressed in the CNS, inhibition of spinal PGE_2 production by NSAIDs that inhibit COX-2 may be an essential mechanism in preventing the establishment of hyperalgesia. The effect of NSAIDs on both central and peripheral PG synthesis suggests that these compounds have an essential role in multimodal analgesic protocols.

The dose and pharmacokinetic parameters of the commonly used NSAIDs in the US are summarized inTable 1 (Coetzee., 2013).

Table 1. The dose and pharmacokinetic parameters of the commonly used NSAIDs in the U.S.

Drug	Approved Species	Indications	Dose (Cattle)	T ½ in Cattle	Withhold Period
Flunixin meglumine (Merck)	Cattle, horses, and pigs	Antipyretic, Anti-inflammatory,	2.2 mg/kg IV 3.3 mg/kg	3-8 h Longer in topical	Meat-4 d (IV) Meat-8 d (topical)

		BRD, and mastitis Footrot pain	Topical		Milk-36 h
Phenylbutazone	Horses and dogs	Anti-inflammatory	4 mg/kg IV ONLY!	40-55 h	Not approved for cattle in the U.S.
Ketoprofen (Zoetis)	Horses and dogs	Anti-inflammatory	1.5 mg/kg IV, IM	0.42 h	Only approved for cattle when co-administered with tulathromycin (Draxxin KP ®)
Aspirin (Generic)	No FDA approval Horses and cattle	Reduction of fever, relief of minor aches and joint pain	50-100 mg/kg PO Oral F < 20%	0.5 h (IV salicylate)	No formal FDA approval. Not for use in lactating cattle
Carprofen (Zoetis)	EU approval for cattle Dogs	Adjunctive therapy of acute respiratory disease and mastitis	1.4 mg/kg body weight IV or SC Oral tablets	Age-dependent < 10 weeks: 49.7 h	Not approved for cattle in the U.S. EU-21 d (meat), 0 d (milk)
Meloxicam (Boehringer Ingelheim)	EU and Canadian approval in cattle Dogs and cats	Adjunctive for BRD; diarrhea and acute mastitis (EU). Analgesia after disbudding (Can)	0.5 IV, SC 0.5-1 mg/k PO Oral F=100%	27 h (Range: 19.97-43.29 h)	Not approved for cattle in the U.S. 15 d EU and 20 d Canada. FARAD 21 d (meat)
Firocoxib (Merial)	Dogs and horses	Anti-inflammatory	0.5 mg/kg (PO) Oral F=98.4%	18.8 h (Range: 14.2-25.5 h)	Not approved for cattle in the U.S. or EU

Meloxicam

Meloxicam is an NSAID of the oxicam class approved in the European Union for adjunctive therapy of acute respiratory disease, diarrhea, and acute mastitis when administered at 0.5 mg/kg IM or SC.Heinrich and others demonstrated that 0.5 mg/ kg meloxicam IM combined with a cornual nerve block reduced serum cortisol response for longer than calves receiving only local

anesthesia before cautery dehorning (Heinrich et al., 2009). Furthermore, calves receiving meloxicam had lower heart and respiratory rates than placebo-treated control calves over 24 hours post-dehorning (Coetzee et al., 2012). Stewart and others found that meloxicam administered IV at 0.5 mg/kg mitigated the onset of pain responses as measured by heart rate variability and eye temperature, compared with a cornual nerve block administration (Stewart el al., 2009).Coetzee and others observed that meloxicam administered at 0.5 mg/kg IV prior to dehorning in 16-week-old calves reduced plasma substance P concentrations and improved weight gain over ten days compared with untreated controls (Coetzee et al., 2012).These reports demonstrate that administration of meloxicam prior to dehorning at 0.5 mg/kg IV or IM may be effective at alleviating pain and distress associated with painful procedures in cattle.

The pharmacokinetics of meloxicam after oral and IV administration have recently been described (Coetzee et al., 2009; Coetzee et al., 2011). A mean peak plasma concentration (Cmax) of 3.10 ug/mL (Range: 2.64 – 3.79 ug/mL) was recorded at 11.64 hours (Range: 10 – 12 hours) with a half-life (T ½ λz) of 27.54 hours (Range: 19.97 – 43.29 hours) after oral meloxicam administration. The bioavailability (F) of oral meloxicam corrected for dose was 1.00 (Range: 0.64 – 1.66).These findings indicate that oral meloxicam administration could effectively and conveniently provide long-lasting analgesia to ruminant calves.

Meloxicam (20 mg/ml) is approved for use in cattle in several European countries with a 15-day meat withdrawal time and a 5-day milk withdrawal time following administration of 0.5 mg/kg IM or SC.An oral meloxicam suspension (1.5 mg/mL) and injectable formulation (5 mg/mL) are approved in the United States to control pain and inflammation associated with osteoarthritis in dogs. Furthermore, an injectable formulation (5 mg/ml) is approved to control post-operative pain and inflammation in cats.Several inexpensive generic tablet formulations

containing meloxicam (7.5 and 15 mg) have recently been approved to relieve signs and symptoms of osteoarthritis in human medicine. In the absence of FDA-approved analgesic compounds in food animals, the use of oral meloxicam tablets to alleviate pain in cattle could be considered under AMDUCA. Research data support a 21-d meat withhold period and a 4-d milk withhold period in late lactation dairy cattle (Coetzee et al., 2015). A longer withhold period has been suggested in early lactation dairy cows (Gorden et al., 2018).Practitioners are advised to contact FARAD for the most up-to-date withhold period recommendations.

Transdermal Flunixin (Banamine Transdermal®, Merck Inc.)

On July 25, 2017, the US Food and Drug Administration announced the approval of Banamine Transdermal (flunixin transdermal solution), an animal drug approved for the control of pain associated with foot rot and the control of pyrexia (fever) associated with bovine respiratory disease. The pharmacokinetics of transdermal flunixin (FTD) in calves and dairy cows have been described by Kleinhenz and others (Kleinhenz et al., 2016; Kleinhenz et al., 2017). In calves, transdermal flunixin could be detected at the first time point (10 min), indicating transdermal flunixin is rapidly absorbed. The time to maximum concentration was approximately twohours with a half-life of 6.4 hours. The authors report a bioavailability of 48% in calves.

FTD has comparable reported pharmacokinetics to other routes of administration. Despite having the lowest bioavailability, it has a maximum concentration comparable to subcutaneous and oral dosing (TD 1.2 µg/mL; SQ 1.3 µg/mL; PO 0.9 µg/mL). The half-life of FTD is slightly longer (6.4 h) than that of the extravascular routes (IM 4.5 h, SQ 5.4h) of administration (Kleinhenz et al., 2016).

Since dosing transdermal flunixin is very convenient with minimal restraint, a pharmacokinetic study investigating FTD occurred. In Holstein cows (mature, lactating females), three doses of FTD were studied (Kleinhenz et al., 2019). Cows received three label doses of FTD (3.33 mg/kg; 1 mL/15kg) at 24-h intervals. Following the three doses, the half-life was 5.2 h, with maximum plasma concentrations reached at 2.8 h. However, the time range to maximum concentrations was 1 to 8 h. When dosed at 24-hour intervals, no plasma accumulation was observed.

In a European study, FTD suppresses prostaglandin E_2 (PGE_2) production for 48 h. In this study, suppression of PGE2 was determined using an inflammatory exudate model, with an 80% reduction seen out to 48 h (Thiry et al., 2017). In data from the author's lab using a whole blood ex vivo model, PGE2 production decreased to 30 h (Kleinhenz et al., 2018). Thus, one can expect to see anti-inflammatory actions of FTD out to 30 h.

Dehorning

Only studies investigating FTD without a local anesthetic block at the time of dehorning have been published (Kleinhenz et al., 2018). In that study, 8-week-old calves were hot-iron dehorned and followed for 72 h. Outcome measures collected include mechanical nociception threshold testing, plasma cortisol, ocular thermography, and substance P. Calves treated with FTD at dehorning had lower cortisol levels than placebo controls. The MNT scores taken around the horn tissue were not different, but MNT taken at a central location were higher at 48 h post-dehorning. Thus, FTD may have effects in decreasing central sensitization. There were no differences in substance P levels among treatment groups. Further work is needed to determine

FTD's role in a multi-modal analgesic plan. This plan should include dose timing relative to dehorning and local anesthetic block.

Castration

The use of FTD at the time of surgical castration has been described (Kleinhenz et al., 2018). Although the FTD did not inhibit a spike in cortisol associated with castration, it lowered cortisol levelstwohours post-castration. This cortisol lowering may be beneficial when castration is done at arrival, and vaccines are concurrently administered. A floor-based pressure mat system was used to analyze the gait of calves following castration. No benefit of FTD was seen between castration groups (placebo vs. FTD); however, the castrated groups showed evidence of altering their gait following castration. Specifically, the castrated calves increased force on their frontal limbs following castration. This indicated they preferentially shifted their weight away from the castration site. Additionally, a significant difference in the impulse was observed. This difference was attributed to the sham castrated steers moving faster across the mat. No differences in substance P were seen between groups.

Lameness

As previously mentioned, FTD is the only drug with a label for pain control in cattle. The label is specific for the pain associated with foot rot. Thus, pain associated with any other lameness modality (sole ulcer, arthritis/synovitis) would still constitute an extra-label drug use. Additionally, FTD is not approved for adult dairy cattle, which have a high prevalence of lameness. In an experiment conducted before FTD’s label approval for pain control, adult dairy cows were subjected to lameness using an amphotericin B model and treated with FTD for

threedoses at 24-hour intervals (Kleinhenz et al., 2019). The model induces local arthritis/synovitis in the joint where the amphotericin B is instilled. Cows in this study were compared to lame placebo controls and non-lame placebo controls. Outcomes measured included plasma cortisol, substance P, temperature of the coronary band via thermography, MNT testing, and gait analysis. Cows in the LAME groups were visually lame (2/5) following induction, with the FTD-treated cows being more lame. After 72 h, there were no lame cows in the FTD group, but 4/10 lame cows in the placebo group. Furthermore, FTD-treated cows had MNT scores that approached pre-lameness levels by 48 h post-dosing. Thus, FTD does provide some analgesic benefits to lame cows. However, no changes were observed in the gait analysis using the floor-based pressure mat. Another conclusion drawn from comparing the MNT data and visual lameness scores is that cows may still be painful despite having a normal gait and lameness score.

Aspirin

Despite its over-the-counter availability and widespread use for controlling fever and minor pains, aspirin has no formal FDA approval. As such, it is not recommended for use in food animals by the Food Animal Residue Avoidance Databank (FARAD). Recently, we investigated the pharmacokinetics of salicylic acid (SA) in the milk and plasma of postpartum dairy cows after oral administration of acetylsalicylic acid (ASA) (Fritz et al., 2022). The research aimed to estimate a recommended milk withdrawal period for dairy cows treated with ASA and determine the impact of ASA administration on plasma prostaglandin E2 metabolite (PGEM) concentrations. The results showed that all cows' SA concentrations were undetected 48 hours after the last ASA treatment. However, after this period, a secondary peak was observed in both

plasma and milk. These data show that the milk withdrawal period was 168 hours (7 days). Additionally, plasma PGEM concentrations were reduced for up to 12 hours after ASA administration. The findings suggest that the current milk withhold recommendation for dairy cattle administered ASA may need revision to 168 hours. ASA administration may mitigate postpartum inflammation by reducing prostaglandin production for up to 12 hours after treatment. Further research is needed to understand the basis of secondary SA peaks and elucidate the long-term effects of ASA administration on dairy cow health.

Prospects for Treating Chronic Pain and Central Sensitization in Cattle

Gabapentin

Gabapentin (1-(aminomethyl) cyclohexane acetic acid) is a γ-aminobutyric acid (GABA) analoginitially developed for the treatment of spastic disorders and epilepsy. Studies have reported that gabapentin is also effective for the management of chronic pain or inflammation of neuropathic origin. Although the mechanism of action of gabapentin is poorly understood, it is thought to bind to the α2-δ subunit of voltage-gated calcium channels acting pre-synaptically to decrease the release of excitatory neurotransmitters. Efficacy of gabapentin in humans is associated with 2 μg/mL plasma drug concentrations. It has also been reported that gabapentin can interact synergistically with NSAIDs to produce anti-hyperalgesic effects. In a recent study we report a mean peak plasma gabapentin concentration (Cmax) of 3.40 μg/mL (Range: 1.70 to 4.60 μg/mL) at 7.20 h (Range: 6 to 10 h) after oral gabapentin administration at 15 mg/ kg. An elimination half-life (T ½ λz) of 7.9 h (Range: 6.9 to 12.4 h) was recorded. Oral administration of gabapentin at 15 mg/kg may be associated with plasma concentrations of >2 μg/mL for up to 15 h. The pharmacokinetics of gabapentin suggest that this compound may be useful in mitigating chronic neuropathic and inflammatory pain in ruminant cattle (Malreddy et al., 2013).

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