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WELFARE AND BEHAVIOR: *Invited Review*

Invited Review: On-farm pain management of food production animals

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ABSTRACT

Purpose: The purpose of this review was to describe the current options and unmet needs for on-farm pain control in food production animals.

Sources: Peer-reviewed literature was the primary source of data and information for this review.

Synthesis: There are millions of farm animals that experience painful livestock management procedures each year. Moreover, disease conditions such as lameness require on-farm analgesic treatment. Consumer concerns about the welfare of food animals experiencing painful procedures have increased the requirement for producers to implement pain management protocols on farms. However, objective pain evaluation methods are lacking, making it difficult to identify animals in pain and to secure regulatory approval of analgesics for livestock. Flunixin, meloxicam, and ketoprofen are nonsteroidal anti-inflammatory drugs with supporting research for on-farm analgesia. An understanding of their pharmacological properties and effects in animals, regulatory restrictions such as meat withholds, costs, and dosing requirements are needed to make the most prudent drug choice.

Conclusions and Applications: Options for on-farm analgesia are limited, and further research is needed on simple and objective ways to measure pain in food animals. The use of local anesthetics and nonsteroidal anti-inflammatory drugs such as flunixin or meloxicam are currently the best options for on-farm analgesia.

Key words: analgesia, pain, bovine, swine

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INTRODUCTION

It is well established that farm animals are capable of experiencing pain. The pain experienced by food animals may be the result of animal management procedures, such as castration, dehorning, and tail docking, or medical conditions, such as lameness and dystocia. Many of these procedures are performed on farm without the use of analgesics or anesthetics for pain management. The American Veterinary Medical Association, American Association of Bovine Practitioners, and American Association of Swine Veterinarians have all developed position statements recommending analgesic use in food animals following painful procedures. Furthermore, consumers are becoming more aware and concerned about the welfare and well-being of animals raised for food. This has increased pressure on suppliers to ensure animals entering their systems are treated humanely.

Unfortunately, a challenge with on-farm pain management in the United States is the lack of approved therapeutics. To date, in the United States, there is only one drug approved for control of pain associated with interdigital phlegmon (foot rot) in nonlactating cattle. Therefore, use of drugs for pain management during elective procedures such as dehorning and castration in cattle, or to provide analgesia in lactating dairy cows and swine, is considered extra-label drug use and is regulated in accordance with the Animal Medicinal Drug Use Clarification Act. In other countries, there are approved analgesics, but they are not always used at the time of the painful procedure or event (Moggy et al., 2017). The use of alternative and preventive strategies has been explored, but few strategies have gained widespread acceptance.

The objectives of this review were to briefly describe pain assessment and challenges in providing pain mitigation to food production animals and to describe on-farm pain mitigation strategies with a focus on pharmacologic interventions.

PAIN ASSESSMENT IN FOOD ANIMALS

Pain assessment in cattle and swine is difficult as they are stoic by nature and conceal pain behaviors. For the approval of analgesics in cattle and swine, the US Food and Drug Administration (**US FDA**) has provided guidance recommending that validated methods of pain assessment be used in the target species (US FDA, 2006). Outcome measures for pain assessment must be (1) objective, (2) repeatable, and (3) clearly defined (US FDA, 2006). In previous research, markers for the evaluation of pain and distress associated with noxious animal husbandry procedures have focused on assessing behavioral, physiological, and neuroendocrine changes. Changes in animal behavior have been assessed using visual pen behavior scoring, videography, facial grimace scoring, accelerometers, mechanical nociception threshold testing, condition place aversion, and gait analysis through the use of pressure mats (Coetzee, 2013; Kleinhenz et al., 2018; Ede et al., 2019). Physiological changes have been assessed using serum cortisol measurement, heart rate determination, feed intake and ADG. Neuroendocrine changes have been assessed through measurement of the neuropeptide substance P, infrared thermography, heart rate variability, and electroencephalography (Coetzee, 2011). Of these outcomes, behavioral scoring, pressure mats for gait analysis, and cranial thermography have shown the greatest promise for field applications.

To date, the combination of behavioral scoring with pressure mat gait analysis has proven to be the optimal pain assessment outcomes for FDA approval. Pressure mat gait analysis uses a floor-based mat that records and analyzes the contact force, contact area, and stance time for each limb as an animal walks. Pressure mat gait analysis was employed to support the approval of transdermal flunixin for control of pain associated with foot rot (US FDA, 2017). Cattle treated with transdermal flunixin placed increased total contact force and had greater contact area for the limbs with experimentally induced foot rot. The pressure mat gait analysis has also been deployed to assess pain associated with lameness in cattle and swine, castration in cattle, and parturition in cattle. Following surgical castration, cattle place more force on their front limbs, indicating a shift in weigh distribution (Kleinhenz et al., 2018). A similar shift in weight distribution is seen in dairy cows following unassisted calving. Cows treated with oral meloxicam placed more weight on the rear limb compared with placebo-treated cows (Kleinhenz et al., 2019a). Meloxicam-treated cows had shorter stride lengths measured by video camera compared with placebo-treated cows. The authors attributed this to meloxicam reducing the pain associated with udder edema similar to cows with mastitis (Fitzpatrick et al., 2013).

CHALLENGES IN FOOD ANIMAL ANALGESIA

There are numerous challenges associated with providing analgesia to food production animals. These challenges include the lack of approved medications, regulatory concerns, delayed onset of action, short duration of action, the need to handle animals repeatedly and the cost of the analgesic, and the associated meat and milk withhold periods. With the exception of the use of transdermal flunixin for the control of pain associated with interdigital phlegmon in cattle, medications dispensed for pain control are used in an extra-label manner under the Animal Medicinal Drug Use Clarification Act of 1994 (US FDA, 1994). To use drugs in an extra-label manner, specific conditions must be met. These conditions include the following: (1) the extra-label drug use (**ELDU**) must be under a veterinary-client-patient relationship; (2) ELDU is only allowed for FDA-approved animal and human drugs; (3) ELDU is only permitted when the health or well-being of the animal is threatened and not for production purposes; (4) ELDU in feed is prohibited; and (5) the ELDU cannot result in a violative drug residue in food intended for human consumption.

There is a delay in onset for most analgesic drugs, and their duration of action is relatively short with effects lasting only hours. This presents a challenge to producers and veterinarians as it may result in the need for additional doses as it has been documented that animals may be experiencing pain for days following the painful procedure (Adcock et al., 2020). These characteristics will be discussed in more depth later in the review, but it should be noted that local anesthetics require 5 to 10 min to reach full effect and last for less than 4 h. The time for nonsteroidal anti-inflammatory drugs (**NSAID**) to take effect is longer compared with local anesthetics, but their duration of action is longer. However, each NSAID has individual properties. For example, meloxicam takes up to 12 h to reach full effect but lasts up to 48 h. This is in contrast to flunixin, which acts rapidly but has a duration of action of under 24 h.

Producers must account for the time required to perform the procedure, the time required to administer the analgesic drug(s), and the time required for onset of analgesic action. These delays may require animals to be handled longer, be handled additional times, or undergo the procedure without full benefit of the analgesia. The additional costs of drugs and labor must also be considered for on-farm pain management. Additional labor costs have been cited as a barrier to implementation of on-farm analgesic protocols (Moggy et al., 2017). Finally, the route of administration may require technical training or, in the case of i.m. and s.c. injections, result in pain and tissue damage (Pyorala et al., 1999).

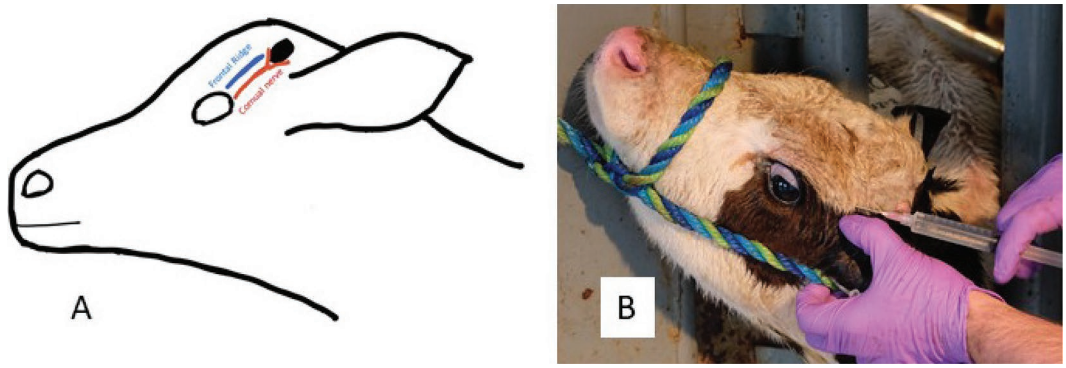

Figure 1. (A) Anatomic location of the cornual nerve (red line) with the landmarks for identifying the correct injection site: the eye, horn bud, and frontal ridge (blue line). (B) Infiltration of 2% lidocaine for local anesthesia of the horn.

PAIN MANAGEMENT FOR ON-FARM PROCEDURES

Dehorning

Dehorning is a common husbandry practice that occurs on the majority of dairy farms and, to a lesser extent, beef farms. Although there is widespread interest in selecting for polled genetics to reduce the need for dehorning in dairy operations, current strategies to increase the percentage of polled Holstein calves may decrease the herd genetic merit (Spurlock et al., 2014). Dehorning is performed to reduce the risk of injury to livestock caregivers and pen mates and to decrease carcass bruising. Dehorned animals also require less bunk space. Regardless of the method used, dehorning has been shown to be painful (Adcock and Tucker, 2018). Calves have been shown to positively respond to lidocaine administered 11 d after dehorning. This indicates the pain associated with dehorning may last for weeks beyond the procedure (Adcock et al., 2020). The American Veterinary Medical Association and American Association of Bovine Practitioners recommend that dehorning take place at the earliest age practicable, and the National Dairy FARM Program 4.0 requires calves to be dehorned by 8 wk of age (National Dairy FARM Program, 2020). Additionally, the National Dairy FARM Program 4.0 requires the use of analgesia at the time of dehorning or disbudding regardless of the method used and age of calf (National Dairy FARM Program, 2020). The same recommendations can be made for goats and sheep that require dehorning or disbudding.

For dehorning, a multimodal analgesic strategy, where a local anesthetic such as lidocaine is used in combination with an NSAID, is recommended (Winder et al., 2018). This allows for acute pain relief at the time of the procedure as well as decreased inflammation for hours afterward. Lidocaine is a commonly used local anesthetic drug used to manage acute pain due to its rapid onset of action (minutes) and relatively low cost. Blockade of nerve impulses transmitted by the cornual nerve, which innervates the horn area, is easily accomplished by local infiltration of lidocaine or similar agent (Figure 1). Local anesthetics alone have been shown to attenuate acute pain (Winder et al., 2018), but their action lasts less than 4 h after administration. When local anesthetics are administered as the sole analgesic, cortisol levels increased over time compared with controls, indicating a rebound effect as the pharmacological effects diminish (Allen et al., 2013; Winder et al., 2018). A potential negative side effect of lidocaine administration is the risk of increased hemorrhage due to the drug causing vasodilation.

Nonsteroidal anti-inflammatory drugs are commonly used to provide analgesia and reduce inflammation associated with dehorning. Flunixin meglumine has US FDA approval for reduction of fever, inflammation, and pain associated with foot rot in cattle. Flunixin meglumine provides up to 6 h of analgesia when used with a local anesthetic nerve block. When used at the time of dehorning, transdermal flunixin provides for decreased cortisol levels compared with controls and improvement in mechanical nociception threshold tests at control sites, indicating reduction in central sensitization (Kleinhenz et al., 2017).

An injectable formulation of meloxicam is approved in Canada for pain control after dehorning. In the United States, human generic meloxicam tablets can be administered in an extra-label manner. There are several studies supporting the use of meloxicam for dehorning pain control. Meloxicam has been shown to improve mechanical nociception threshold tests 24 h after dehorning (Heinrich et al., 2010). Meloxicam has also been shown to lower cortisol and substance P in calves 8 to 10 wk of age (Glynn et al., 2013). In calves undergoing amputation dehorning at 6 mo of age, meloxicam-treated calves had improved ADG over 10 d after the procedure (Allen et al., 2013). Recent data have revealed meloxicam-treated calves were less averse to spending time in the pen in which they were disbudded compared with pens they were not disbudded (Ede et al., 2019).

Ketoprofen is approved in Canada for pain control associated with a variety of conditions but not dehorning. It has been evaluated for dehorning analgesia. When administered in combination with a local anesthetic, ketoprofen ameliorated the acute cortisol response (McMeekan et al., 1998; Sutherland et al., 2002; Milligan et al., 2004; Duffield et al., 2010). Ketoprofen improved mechanical nociception threshold measures when given at 3 mg/kg by i.m. injections in conjunction with a topical local anesthetic (Espinoza et al., 2015). A negative attribute of ketoprofen is its short duration of action, and thus, it is not a suitable choice for dehorning pain (Ede et al., 2019).

Carprofen and firocoxib have both been evaluated for dehorning pain control. Carprofen is approved in the European Union for pain. A study investigating oral carprofen did not show analgesic benefit (Stock et al., 2016). Similarly, Stock et al. (2015) observed firocoxib given at 1 mg/kg orally did not provide analgesia despite evidence of anti-inflammatory action based on lower prostaglandin E_2 production. Studies comparing NSAID side by side are lacking in the literature.

Branding

Branding is a common management practice on beef operations especially in the western part of Canada and the United States (USDA, Animal and Plant Health Inspection Service, 2008; Moggy et al., 2017). In a Canadian survey, branding was practiced on half of the farms, but analgesia was provided on less than 5% (Moggy et al., 2017). Both hot-iron and freeze branding have been shown to induce pain that lasts for extended periods of time (Lay et al., 1992; Schwartzkopf-Genswein et al., 1997; Tucker et al., 2014a). Despite the evidence that branding is painful, there are few studies in the published literature regarding analgesic strategies at the time of branding. Of those, a single dose of flunixin at 1.1 mg/kg did not provide adequate analgesia (Tucker et al., 2014b). This is not surprising as flunixin, given at the high end of the label dose of 2.2 mg/kg by i.v. administration, has a relatively short half-life. Meloxicam given at 0.5 mg/kg subcutaneously at the time of concurrent surgical castration provided analgesia based on improved pain behaviors of increased lying time, decreased tail flicks, and less head turning (Melendez et al., 2018b).

Bovine Castration

Castration is performed on male food animals to minimize male aggressive behaviors, improve carcass quality, and eliminate the risk of unwanted pregnancies in the feeding period. Regardless of the animal's age and technique used, castration causes pain, distress, and other behavioral and neuroendocrine changes (Coetzee et al., 2017). Alternatives such as immunocastration have been demonstrated to be effective (Hirsbrunner et al., 2017). However, this technique has not gained wide-spread adoption due to lack of product approvals, the need for repeated injection, and risk of human health implications due to vaccine exposure.

Similar to dehorning, a multimodal analgesic strategy has been shown to be the most beneficial to reduce pain during castration. Local anesthetics on their own reduced cortisol compared with controls undergoing castration but had little effect on ADG, feed intake, or inflammatory mediators (Earley and Crowe, 2002; Ting et al., 2003a,b; Webster et al., 2013). Local anesthetic action is potentiated by co-administration of an NSAID (Nordi et al., 2019).

Calves administered flunixin and lidocaine also had lower salivary cortisol and pain scores compared with placebo controls (Nordi et al., 2019). Calves treated with flunixin and given lidocaine as a local anesthetic at the time of castration had greater DMI compared with flunixin only–treated calves (Coetzee, 2013; Nordi et al., 2019). Flunixin-treated calves also had longer stride lengths following surgical castration compared with controls, suggesting flunixin reduced pain at the castration cite, allowing for longer distances between steps (Currah et al., 2009). The transdermal flunixin formulation, without a local anesthetic, reduced plasma cortisol up to 8 h after the procedure compared with placebo controls but provided negligible evidence of analgesia based on substance P and pressure mat gait analysis (Kleinhenz et al., 2018).

Meloxicam has been evaluated for pain control from surgical and nonsurgical (band) castration. Additionally, meloxicam is approved for the control of pain following castration in Canada. Meloxicam-treated calves had a reduced inflammatory response compared with placebo controls based on lower salivary cortisol levels, white blood cell counts, and reduced acute phase protein responses when administered meloxicam (Melendez et al., 2018a). Interestingly, no additional benefit was observed when meloxicam was administered with lidocaine (Melendez et al., 2018a).

Processing Procedures on Pig Farms

Piglets undergo several processing procedures during their first week of life, including surgical castration, tail docking, teeth clipping, and ear tagging or notching for identification. Surgical castration eliminates boar taint (i.e., improves meat quality) and reduces aggression (Hay et al., 2003). Tail docking reduces the occurrence and severity of injury associated with tail biting (Sutherland et al., 2008). Teeth clipping, or removal of the piglet's third incisors and canine teeth, is done to reduce tissue damage associated with interpig aggression and to decrease lacerations to the sow's udder (Sutherland, 2015). However, previous work has challenged this, finding minimal association between teeth clipping and lesion incidence or severity on sows and piglets (Holyoake et al., 2004; Fu et al., 2019). The implications of teeth clipping on pig welfare (e.g., increased stress; pain; and risk of gum damage, abscesses, and infection) and production appear to outweigh the benefits (Sutherland, 2015), and many pig producers in North America are electing to leave needle teeth intact, clipping only when necessary (AVMA, 2010; NFACC, 2014).

Alternatives to traditional surgical castration have been reported. A gonadotropin-releasing factor analog vaccine has been approved by the FDA for the temporary immunocastration of boars (US FDA, 2011). Although approved for use in swine, the need for repeated vaccination and the risk of human health implications due to vaccine exposure have slowed its adoption. Recently, a pilot study using a CO_2 laser scalpel was reported as an alternative to traditional surgical castration (Viscardi et al., 2020). There were no observed differences in wound healing or pain biomarkers. The authors report thermal damage of the laser-castrated piglets as a possible factor in the lack of differences (Viscardi et al., 2020).

Piglet processing procedures are known to be painful; however, without approved analgesia options in the United States, pain management is not routinely provided. In Canada and countries in the European Union, analgesia administration is required for postoperative pain management of piglets undergoing surgical castration and tail docking (European Commission, 2010; NFACC, 2014). As with all food animals, the most common class of analgesics given to pigs to alleviate pain are NSAID.

Meloxicam (0.4 mg/kg) is the only NSAID labeled for swine to relieve pain associated with minor soft tissue surgery in Canada. Meloxicam can be administered to pigs on farm orally or via an i.m. injection. Previous studies have reported that an i.m. injection of meloxicam was successful in providing pain relief to piglets after surgical castration, noting a reduction in blood cortisol concentration and decreased pain-related behaviors postoperatively (0.4 mg/kg; Keita et al., 2010; Kluivers-Poodt et al., 2013; 0.06 mL/piglet: Gottardo et al., 2016). Oral meloxicam (30 mg/kg) administered to the sow and delivered transmammary to her nursing piglets also provided analgesia after surgical castration and tail docking, as evidenced by a decrease in blood cortisol and prostaglandin E_2 concentration, and maintenance of cranial skin temperature (Bates et al., 2014). However, these results have been contradicted by other studies, which have indicated that an i.m. injection of meloxicam (0.4–1.0 mg/kg) was ineffective at alleviating pain associated with piglet processing procedures (castration: Kluivers-Poodt et al., 2012; Viscardi and Turner, 2018a; Yun et al., 2019; tail docking: Herskin et al., 2016; Viscardi and Turner, 2019a). The inconsistent results following meloxicam use to alleviate piglet pain suggests more work may be needed to optimize drug dose, route and time of administration, as well as study design and outcome measures to ensure drug efficacy before making recommendations.

Ketoprofen (approved in Canada only) and flunixin meglumine (approved in Canada and the United States) are NSAID labeled to treat fever and respiratory disease in swine; however, there is limited research on their ability to reduce postprocedural pain in piglets. Cassar et al. (2014) found 3.0 mg/kg ketoprofen, administered intramuscularly, reduced blood cortisol levels of piglets up to 4 h after castration. In another study, piglets given the same dose of ketoprofen intramuscularly before surgical castration were able to navigate a chute faster than castrated piglets not given an NSAID (Reynolds et al., 2020). However, Viscardi and Turner (2018a) found that administration of ketoprofen (6.0 mg/kg i.m.) did not significantly reduce piglet pain behaviors or facial grimacing after castration. Similarly, flunixin meglumine (no dose noted), administered intramuscularly, did not reduce castration-associated vocalizations, pain behaviors, or the cortisol response after the procedure (Sutherland et al., 2012). A recent pharmacokinetic study in preweaned piglets found flunixin meglumine (3.3 mg/kg, oral and i.m.) achieved therapeutic concentration ranges that have provided appropriate pain management to adult pigs; however, a transdermal application of flunixin resulted in very low plasma drug concentrations, unlikely to effectively alleviate postoperative pain (Kittrell et al., 2020). Future work should determine whether 3.3 mg/kg (oral or i.m.) of flunixin can reduce behavioral and physiological signs of pain in piglets after processing.

Lidocaine, a local anesthetic, decreased procedure-associated vocalizations and defense behavior and reduced plasma cortisol levels of piglets after castration when preemptively injected into each testicle (0.5–1.0 mL; Marx et al., 2003; Hansson et al., 2011; Kluivers-Poodt et al., 2012). Similarly, a s.c. injection of 0.3 mL of lidocaine into the base of the tail reduced vocalizations and defensive movements of piglets at the time of tail docking but did not reduce postprocedural pain behaviors (Herskin et al., 2016). The routes of administration described (subcutaneous and intratesticular) are much more technical than those described for NSAID, which reduces the practicality of lidocaine use on farm. The route of administration may also cause more distress to piglets, due to prolonged handling and increased pain, while providing limited postoperative pain relief (Leidig et al., 2009; Hansson et al., 2011). Topical anesthetics have been used to reduce processing procedure–associated pain in piglets, with limited efficacy. Cetacaine (14% benzaine, 2% butamben, and 2% tetracaine hydrochloride; Cetylite Inc., Pennsauken, NJ) or Tri-Solfen (40.6 g/L lignocaine, 4.5 g/L bupivacaine, 24.8 mg/L adrenaline, and 5.0 g/L cetrimide; Bayer Australia Ltd., Pymble, NSW, Australia) were administered topically onto the spermatic cords before they were cut during piglet surgical castration in a study conducted by Sutherland et al. (2010). Neither treatment significantly reduced plasma cortisol concentrations, stress vocalizations, or pain behaviors after castration (Sutherland et al., 2010). Recent contradictory studies found Tri-Solfen was effective at mitigating acute peri-operative castration pain in piglets (Lomax et al., 2017; Sheil et al., 2020). It appears more work is needed to verify Tri-Solfen anesthesia efficacy (this product is currently unavailable in North America). EMLA (a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine; APP Pharmaceuticals LLC, Schaumburg, IL) cream or Maxilene (4% lidocaine; RGR Pharma Ltd., LaSalle, Ontario, Canada) applied topically to the scrotum or tail of piglets before surgical castration or tail docking, respectively, were not able to reduce procedure-associated vocalizations or postoperative pain behavior and facial grimacing (Viscardi et al., 2017; Viscardi and Turner, 2018a,b). Based on their short duration of action and minimal analgesic effects, it is unlikely that a topical anesthetic alone will be able to provide sufficient pain management for piglets undergoing processing procedures.

A multimodal approach to piglet pain management, with a local anesthetic and an NSAID, may be the most effective option to alleviate processing-procedure pain. Bonastre et al. (2016) found lidocaine (0.4 mL, intratesticular) and meloxicam (0.4 mg/kg i.m.) significantly decreased cortisol concentrations of piglets after castration. Similar results were found by Hansson et al. (2011), using 0.5 mL intratesticular injection of lidocaine (10 mg/mL) combined with epinephrine (5.0 μg/mL), and meloxicam (0.2 mL/piglet, i.m.) before surgical castration; piglets had reduced procedure-associated vocalizations and less observed pain behaviors. Unfortunately, these are not practical options for on-farm use, primary because of the cost, time, and effort needed to administer both an anesthetic and analgesic at the time of processing. Buprenorphine (an opioid) alone was found to effectively reduce postcastration pain behaviors and facial grimacing in piglets (Viscardi and Turner, 2018b); however, this is an even less practical on-farm option, due to restrictions associated with obtaining and administering a controlled substance.

Authors of a systematic review of the pain management literature for piglets undergoing routine processing procedures were not able to make strong recommendations due to the low-quality evidence in the literature (O'Connor et al., 2014). It was evident that more work is needed to determine effective pain management strategies for neonatal pigs. Recently, our group described administering firocoxib to sows for pain mitigation in piglets undergoing routine neonatal processing. Barrows nursing sows administered firocoxib at 2 mg/kg by i.m. injection had lower cortisol concentrations compared with controls and sows receiving a lower dose of firocoxib (Coetzee et al., 2019). Additionally, piglets nursing from sows receiving 2 mg/kg firocoxib by i.m. injection had improved weight gains. These findings suggest that firocoxib, passed from the sow to piglets in the milk, may safely reduce stress and enhance production by increased weight gains.

Lameness

Lameness is a relatively common disease condition of cattle and swine. Unlike the painful procedures discussed previously in this review; the onset of lameness associated pain is typically unknown. Lameness rates vary by farm with reported prevalence ranging from 6.9 to 54.8% (von Keyserlingk et al., 2012; Adams et al., 2017). Furthermore, lameness has been observed to be under-reported by producers when compared with independent observers (Wells et al., 1993; Whay et al., 2003). There are known economic and production losses seen with lameness in addition to pain and distress. Lameness in the United States has been estimated to cost between \$120 and \$216 per case (Cha et al., 2010). Due to the visible changes in animal movement, the evaluation of lameness prevalence is included in third party animal welfare audits (National Dairy FARM Program, 2020).

Causes of lameness include both infectious and noninfectious etiologies. It is important to note that infectious and noninfectious etiologies may both be present in cases of lameness. Common infectious etiologies are foot rot (interdigital phlegmon) and digital dermatitis in cattle and *Streptococcus suis* in swine. Noninfectious causes include laminitis, defects in the horny tissue, such as sole ulcers or white line disease, and fractures of any bones of the limb. Due to the nature of lameness, treatment recommendations include a multimodal approach. These approaches include trimming of the diseased hoof, application of hoof blocks to sound toes, systemic or local antibiotics, and analgesics (Coetzee et al., 2017).

Early lameness detection is ideal for the obvious animal welfare implications but also for prevention of central sensitization. Central sensitization can lead to increased sensitivity of pain (hyperalgesia) or pain from nonpainful stimuli (allodynia; Anderson and Muir, 2005). Unlike dehorning or castration, pre-emptive analgesia, that has the potential to block central sensitization, is not possible with lameness.

Transdermal flunixin is approved for the control of pain associated with lameness and is the only FDA-approved pain medication for food animals in the United States. In the United States, the label claim is specific for the control of pain associated with foot rot. According to documentation supporting the approval of transdermal flunixin, calves treated at the dose of 3.3 mg/kg had improved lameness scores and increased contact force when walking across a pressure mat (US FDA, 2017). A study investigating transdermal flunixin at the label dose of 3.3 mg/kg administered to lactating dairy cattle for 3 treatments using an amphotericin B arthritis/synovitis lameness model reported flunixin-treated cows had lower joint temperatures as measured by infrared thermography and improved mechanical nociception threshold measures (Kleinhenz et al., 2019b). However, these improvements were not seen until after the second dose was administered. No differences in pressure mat gait outcomes such as contact force or stride length were noted in this study. These results indicate that multiple administrations of transdermal flunixin may be required to provide analgesia to cattle with lameness.

Flunixin meglumine administered by i.v. injection has also been investigated in lameness models and clinical field trials (Schulz et al., 2011; Chapinal et al., 2014; Wagner et al., 2017). Calves receiving i.v. flunixin following lameness induction using amphotericin B had improved lameness scores compared with controls (Schulz et al., 2011). Additionally, flunixin-treated cattle had an increase in contact pressure and surface area of the affected limb on pressure mat gait analysis. Flunixin-treated cattle spent less time lying compared with placebo cows for the first day. This is likely due to the short half-life of flunixin given intravenously (Gorden et al., 2018).

In a clinical trial, cattle were given flunixin meglumine before corrective hoof trimming and 24 h later. No differences in weight distribution or lameness scores were observed (Chapinal et al., 2010). This study did include nonlame cows in each treatment group and inclusion of these sound cows may have diluted treatment effects. A follow-up by the same research group revealed flunixin-treated cows had decreased weight shifting compared with saline controls. The group then followed only lame cows following a hoof trim and found that flunixin-treated cows had decreased amounts of weight shifting of the rear legs (Wagner et al., 2017). The authors attribute this change to pain alleviation of lame cows by flunixin.

Meloxicam has been shown to improve lameness when given at 0.5 or 1.0 mg/kg orally (Offinger et al., 2013; Nagel et al., 2016). Coetzee et al. (2014) found meloxicam reduced lameness in cattle with experimentally induced lameness based on meloxicam-treated cattle having increased step counts in lame limbs. In that same study, plasma meloxicam concentrations were inversely associated with lameness scores and positively associated with contact pressure on gait analysis. Additionally, meloxicam has been shown to work synergistically with gabapentin (Coetzee et al., 2014). Cattle treated with oral meloxicam and gabapentin had increased stride lengths and applied more force on pressure mat gait analysis compared with placebo-treated controls (Coetzee et al., 2014). Glynn et al. (2013) found that co-administration of meloxicam and gabapentin do not alter either drug's pharmacokinetics.

Ketoprofen has been evaluated for its analgesic benefits in cattle with lameness (Whay et al., 2005; Flower et al., 2008; Chapinal et al., 2010). Cattle receiving ketoprofen at 3 mg/kg had improved gait symmetry and weight distribution (Flower et al., 2008). Chapinal et al. (2014) demonstrated a reduced variation in weight distribution in cattle administered ketoprofen. Furthermore, when included as part of a trim and block treatment regimen, ketoprofen cows had a greater proportion of nonlame cows 35 d later (Thomas et al., 2015). Ketoprofen given intramuscularly for 3 consecutive days prevented the development of hyperalgesia (Whay et al., 2005).

APPLICATIONS

Objective pain assessment in food producing animals remains challenging and is needed to support regulatory approval of analgesic drugs in the United States. In the absence of drugs specifically labeled for pain relief, extra-label drug use will be necessary to address animal welfare concerns related to pain in livestock. This places a regulatory burden on the prescribing veterinarian. Multimodal analgesia, combining an NSAID and local anesthetic, has been the most beneficial for reducing pain associated with on-farm husbandry practices. For cattle undergoing castration, dehorning, or both, meloxicam administered orally (1 mg/kg of BW) or subcutaneously (0.5 mg/kg of BW), in combination with local anesthesia, is currently the preferred analgesic approach based on available scientific evidence. Similar multimodal analgesic approaches have been described in pigs. However, optimizing the timing of drug administration relative to the procedure remains difficult. Transmammary delivery of firocoxib may be a viable option for piglet analgesia at the time of processing. Flunixin, ketoprofen, and meloxicam have been shown to provide temporary pain relief associated with lameness but the addition of gabapentin may be necessary to address chronic pain. Future research is needed to better understand the duration of pain, multi-day pain mitigation strategies, and dosing regimens that are economical and practical.

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