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## **Pain Control in Food Animals** (9-Oct-2003)

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Current attitudes about animal welfare have increased the importance of pain management in livestock. Even minor surgical procedures in livestock are now performed using a combination of regional, local, or general anesthesia combined with uninterrupted post-surgical analgesia. Attitudinal changes toward animal suffering have necessitated an understanding of pain modulation by large animal veterinarians, and a willingness of the owners to incur extra cost in order to comfort animals. Pain is a percept consisting of initial nociception followed by a slower but integrated emotional phase. Nociception is the neural recognition of a potentially injurious physical or chemical stimulus. Pain responses occur only after centralized processing, and elicitation of an emotional output to the nociceptive input. The cerebral cortex, thalamus, and the limbic system are involved in pain processing, so specific behaviors to painful stimuli depend upon species, breed, temperament, and rearing [1,2]. Long-term painful stimuli may enhance sensitivity in some animals, and habituate others. Acute centrally processed pain can be recognized in animals by behavioral changes that include, vacant stare, loss of mobility, guarding or splinting of an affected limb, altered avoidance patterns, vocalization, tachypnea, repetitive motor activities, loss of socialization, repeated attempts at lateral recumbency, inappetence and reduced grooming behavior. The relative importance of these signs in reflecting the degree of pain that is being experienced by an animal is unknown.

### **Neuroanatomy of Pain Pathways**

Nociceptors are axonal termini in the peripheral tissues that discharge in response to painful stimuli. Nociceptors are classified by their sensitivity to particular pain stimuli. **Thermal and pressure** nociceptors are activated by temperature extremes or by the application of a strong force to the tissues. These receptors are dendrites of A $\delta$  neurons whose axons course proximally through the spinal nerves where they synapse on gray matter nociceptive specific neurons in the dorsal horn of the spinal cord. Dorsal horn neurons are arranged in laminae, which are numbered dorsally to ventrally, 1 through 5. Axons of the A $\delta$  neurons synapse in lamina I or onto wide dynamic range neurons of laminae III through V. Axons from both of these post-synaptic neurons enter the white matter of the dorsal and lateral funiculus of the spinal cord, and ascend unsynapsed to the brain through the spinocervical tract. Other axons ascend through spinothalamic tracts that synapse onto thalamocortical neurons in the rostral brainstem [3]. The post-synaptic thalamo-cortical axons course to the brain where impulses are interpreted as a sharp, prickly, acutely painful or burning sensations.

Polymodal Nociceptors are termini of non-myelinated C-type fibers that are activated by thermal, pressure, or mechanical stimuli. The dendrites of the C-type fibers course from their sensory terminus to the dorsal rootlet where they enter the dorsal gray column of the spinal cord. The axons of these fibers synapse on interneurons lying in lamina II, which in turn, synapse on a wide dynamic range neuron in lamina III. Axons of lamina III wide dynamic range neurons ascend the spinal cord to the thalamus where they synapse. Because of the relatively slower conduction rate, and the extra synaptic connection, the signals from the C-type fibers arrive later than that of the A $\delta$  fibers, and the brain interprets the pattern as a dull, aching or throbbing sensation that is termed "deep pain".

Silent Nociceptors are high threshold stretch sensitive neurons in the viscera. Because of the high depolarization threshold, these neurons are silent unless they are subjected to a severe deformation. Axons from the silent nociceptors synapse on the same dorsal horn wide dynamic range neurons as do general somatic afferent neurons from the trunk and the appendicular body. Depolarized silent nociceptors stimulate the shared spinal neurons and give rise to "referred pain" sensations because they are mistakenly interpreted to have originated in the peripheral tissues. Human patients with referred pain interpret discomfort from gastrointestinal or cardiac disease as soreness in the limb or shoulder.

Inhibition and integration of pain signals occur along the entire central nervous system. Peripheral regulation of pain occurs through several mechanisms. Gating is a basic method for pain regulation at the level of the spinal cord. The mechanism of pain gating includes the tactile non-nociceptive A $\beta$  afferents that synapse on inhibitory interneurons of the pain tracts. Pain gating is the most likely explanation for the analgesic properties of a snug bandage, or the temporary relief that is gained by mechanical shaking or rubbing of an acutely injured hand or finger.

Inflammation at the dendritic zone decreases depolarization thresholds of the nociceptors, and enhances pain sensations to stimuli that would not be normally considered noxious. Both C- and A $\delta$  fibers release substance P which increase the rate and the duration of the preganglionic cell discharges. These are interpreted by the brain as enhanced and long-term pain. The sensation of chronic pain may in part be related to these inflammatory mechanisms.

Transmission of pain impulses through the spinal cord are inhibited by descending reflexes that originate in the noradrenergic neurons of the mesencephalic periaqueductal gray matter, and the pontine *locus ceruleus* [4,5]. These nuclear masses are under inhibitory control by neurons of the medial preoptic area of the diencephalon, medial prefrontal cortex, amygdala, and ventral posterior lateral hypothalamus, which express receptors for opioids, glutamate, and NMDA. These neurotransmitters are involved in processing and transmitting pain information from the somesthetic cortex. Stimulation or microinjection of opioids into these areas reduces pain and reflexive activities without dampening pressure, touch, cold and heat sensations.

### **Altered Pain States and Molecular Mechanisms of Pain Sensations**

Heightened pain sensations are classified as either allodynia or hyperalgesia. Patients with allodynia feel pain when they are touched or moved, whereas hyperalgesic patients constantly feel pain. Hyperalgesia is thought to be due to the release of inflammatory mediators that include leukotrienes, prostaglandins, substance P, serotonin, histamine, calcitonin gene related peptides and potassium into the injured site. These molecules initiate inflammation, and recruit other nociceptors. Hypersensitive animals respond poorly to analgesic therapy, especially when treatment is initiated after the onset of the painful stimulus [6]. For instance, sheep with chronic pain have reduced responsiveness to xylazine despite having an increased density of  $\alpha_2$  adrenoceptors on spinal sensory neurons [7].

### **Drug Treatments for Painful Livestock**

Classes of anti-nociceptive drugs that can be administered to food animals include opioids,  $\alpha_2$ -adrenergic agonists, non-steroidal anti-inflammatory drugs, and local anesthetics. The actions and clinical use of these agents are described below.

#### **Opioids**

The natural opioids include the enkephalins, the dynorphins, and the  $\beta$  endorphins. These molecules are synthesized in the spinal cord neurons and adrenal medulla in response to the nociceptive activation of NMDA receptors. NMDA receptor stimulation triggers activation of the c-phos protein which in turn, up-regulates genes encoding the proenkephalins, dynorphin and [Met] enkephalin. Enkephalins, and other opioids inhibit pain transmission by saturable binding to membrane receptors that activate the intramembranous Gi protein, which increases intracellular cyclic AMP, and hyperpolarizes the cell membrane by opening K<sup>+</sup>, and closing Ca<sup>++</sup> channels [3].

Endogenous ligands of the opioid receptors include  $\beta$  endorphin, dynorphin, and enkephalin, which are enzymatic cleavage products of common protopolypeptides, and which bind to  $\mu$ ,  $\kappa$  and  $\delta$  receptors respectively.

Opioids are exogenous molecules that bind  $\mu$ ,  $\kappa$  or  $\delta$  receptors located on the neural cell membranes. Agonists bind to a receptor and produce a measurable cellular effect. Antagonists bind to receptors, but produce no membrane hyperpolarization effect. The hyperpolarizing mechanisms of opioids, are similar to those of their endogenous homologues. Activation of the  $\mu$  receptor also results in depletion of intraneuronal substance P which reduces overall inflammation and neural pain transmission [3].

Most opioids in veterinary use belong to either selective or partially selective  $\mu$  receptor agonists. These include morphine, meperidine, fentanyl, oxymorphone, methadone, buprenorphine and butorphanol [2]. Drugs that bind to, and activate  $\kappa$  receptors are analgesic, but are also dysphoric. Analgesic activities of the  $\kappa$  receptors are probably due to inhibitory activities within the spinal cord pain tracts. Butorphanol, a drug with mixed  $\mu$  and  $\kappa$  affinities, is approved for use in animals, and is commercially available. Because of the adverse behavioral reactions, the pure  $\kappa$  receptor agonists, have not been extensively developed for clinical veterinary use. Pentazocine, an  $\kappa$  agonist has been used for relief of colic pain in

horses, but is no longer commercially available. The  $\delta$  receptor agonists are poor analgesics and are not currently used for treating large animals.

Non-nociceptive Physiologic Effects of  $\mu$  Receptor Agonists - Opioids bind to sympathetic cardiostimulatory neurons in the brainstem resulting in an atropine responsive bradycardia. Animals that are treated with high doses of opioids develop hypoxemia due to decreased responsiveness to carbon dioxide in the medulla. Aortic and carotid body centers are unaffected by  $\mu$  receptor activation. Rapid intravenous infusion of  $\mu$  receptor agonists may produce a peripherally mediated hypotension and tachycardia due to histamine release. Opioids are antitussive due to both  $\kappa$  and  $\mu$  antagonism, but there is little association between antitussive and analgesic activity of an opioid [8].

Opioids increase gastric emptying and intestinal transit times, and are therefore constipating. Intravenous injection of morphine strongly inhibits rumenoreticular contractions for as long as 20 minutes [9]. Ruminants that are treated with high doses of opioids may exhibit tachycardia, and some excitement, but generally do not exhibit the propulsive walking or frantic motor activities that are seen in some other species. Opioids exert anticholinergic activities, and have been used for the symptomatic treatment of diarrhea. Ruminants that are repeatedly treated with opioids develop tolerance, which requires increased drug dosages in order to achieve a desired level of analgesia. Pretreatment of an animal with opioid in anticipation of a painful event provides more analgesia than treatment with the same drug and dosage after robust pain sensations are developed.

Anti-nociceptive Effects of Morphine - Morphine has poor analgesic properties in food animals. It is unclear if the low efficacy is due to a paucity of  $\mu$  receptors in the central nervous system, or to poor drug disposition following parenteral injection. Morphine should be administered parenterally to ruminants because the drug is inactivated by the rumen microflora. Following parenteral injection, morphine has a high volume of distribution, and  $T_{1/2\alpha}$  ranging between 1 and 2 hours. Analgesic plasma concentrations of morphine range between 10 and 30 ng/ml [10]. A 4 to 6 hour treatment interval is necessary in order to achieve continuous therapeutic blood concentrations. After absorption, morphine is rapidly conjugated to the analgesic glucuronide by the liver. Approximately 50% of the total dose is excreted through the bile. Because of morphine's high water solubility, the onset is delayed compared to other  $\mu$  agonist drugs. Conversely, the levels in cerebrospinal fluid (CSF) are more prolonged than in plasma. Unlike the monogastrics, ruminants, do not regurgitate after receiving morphine. Recommended dosage rates of morphine range between 0.05 to 0.1 mg/kg of body weight. In our veterinary hospital, we have given doses as high as 10 mg/kg of body weight to goats, and have observed analgesia that was superior to that seen with lower doses. We do not recommend a voluntary withholding of milk or meat from animals that have been treated parenterally with morphine.

Anti-nociceptive Effects of Fentanyl - Fentanyl is a selective  $\mu$  agonist that is administered parenterally, or transdermally by drug impregnated patches. The drug has a long half-life, and a large volume of distribution due to its lipophilicity. Following parenteral injection, the time of onset of fentanyl is 5 minutes, but the duration of analgesia lasts for only 20 minutes. Fentanyl depresses the respiratory drive, and induces bradycardia. For excretion, fentanyl is dealkylated or demethylated by the lung tissue, and metabolites are further degraded by amide hydrolysis and are excreted in the urine. Skin patches that release fentanyl transdermally at doses of 25, 50, and 100  $\mu$ g/hour are commercially available. The analgesic efficacy of transdermal absorption of fentanyl in ruminants is unclear, however, when applied to swine, analgesic blood concentrations of fentanyl (0.5 and 2 ng/ml) can be reached by 24 hours. The efficacy of fentanyl as an analgesic in ruminants is unclear. Parenteral administration of 5  $\mu$ g/kg of fentanyl to sheep increased the threshold to mechanical stimulation in one study, but had little effect in another [11,12]. Intravenous fentanyl at a dose of 10  $\mu$ g/kg of body weight has been anti-nociceptive to both thermal and pressure stimuli in sheep for 5 to 60 minutes post-dosing [11,12]. Such discrepancies illustrate the need for using clinical rather than experimental models of pain relief. Fentanyl given intravenously to sheep (5  $\mu$ g/kg of body weight) may precipitate a variety of abnormal behaviors that include pica, stall pacing, nystagmus, hyperexcitability, and ataxia [13]. A 3 day meat withholding period is recommended for animals that are treated with fentanyl.

Anti-nociceptive Effects of Buprenorphine - Buprenorphine is a mixed agonist and antagonist with both  $\mu$  and  $\kappa$  affinities. Buprenorphine is poorly absorbed from the gastrointestinal tract, and is weakly reversed by antagonists because of its high affinity and low specificity for the  $\mu$  receptors. There is a 45 minute onset and 240 minute duration of anti-nociceptive activity after a single intravenous dose of buprenorphine [14]. Because of the long period of onset, there is little correlation between the plasma concentration of buprenorphine and amount of analgesia for as long as 45 minutes post-dosing. In sheep, buprenorphine is selectively anti-nociceptive for heat, but not for electrical or mechanical stimuli [15]. One study

found it to be ineffective as an analgesic for electrical stimuli [16]. Buprenorphine treated sheep display repetitive motor activities including propulsive walking, rapid and frequent head movements, chewing, and hypersensitivity to noise or visual stimuli [14]. Buprenorphine has been administered intramuscularly to sheep at doses ranging between 5 and 10 µg/kg of bodyweight every 4 hours. Single buprenorphine doses of 6 µg/kg of body weight had no effect on blood pH, or arterial oxygen tension [15]. The analgesic blood concentrations of buprenorphine range between 189 and 697 pg/ml of plasma. Intravenous dosages  $\geq 10$  µg/kg of body weight are likely to be hyperalgesic due to receptor antagonism. An accurate voluntary withholding time for buprenorphine in food animals is unknown, but probably is similar to that of fentanyl which is 3 days for meat.

Anti-nociceptive Effects of Butorphanol - Butorphanol is probably the most commonly used opiate in livestock. The drug is packaged conveniently for administration to large animals, and has some analgesic efficacy. Anecdotally, some practitioners have indicated that butorphanol enhances appetite. Whether the increased feed intake represents a true appetite stimulation, or an activation of the prehensile and masticatory motor centers is unclear. Nevertheless, the drug is used extensively as a symptomatic treatment for anorexia in the field. Butorphanol has affinity for both  $\mu$  and  $\kappa$  receptors and is a  $\mu$  antagonist and  $\kappa$  agonist. Butorphanol is readily absorbed from parenteral sites, and from the respiratory mucosa, and has a high volume of distribution. The half-time of elimination of butorphanol in the cow ranges between 1 and 2 hours, and drug residues can be detected in milk for as long as 36 hours post-dosing. Tremors, and propulsive walking may occur in cattle that are treated intravenously, but these signs dissipate by 30 minutes after the administration of the drug. Concomitant administration of acepromazine, or an  $\alpha_2$  agonist reduces unwanted motor responses. Butorphanol does not provide regional anesthesia. A clinical study showed that butorphanol enhanced xylazine analgesia in cattle, but the combination was insufficient to fully anesthetize the flank for a standing surgery. Animals that were treated with the combination were apt to lie down during the procedure, and did not have more visceral analgesia than controls that were anesthetized by regional lidocaine infiltration [17]. Intravenous butorphanol (100 µg/kg) produces anti-nociceptive responses to thermal, but not to mechanical stimuli, and in some species, induces greater analgesia for visceral than for superficial pain. The anti-nociception from butorphanol occurs within minutes after intravenous injection, and lasts for as long as 90 minutes post-dosing. Studies that differentiate between superficial and visceral pain relief show the importance of measuring more than one pain modality when testing anti-nociceptive drug efficacy. Recommended dosages of butorphanol for livestock range between 0.02 and 0.25 mg/kg of body weight, either intravenously or subcutaneously. Due to its short half-life, butorphanol treatments must be repeated every 4 hours in order to maintain analgesic concentrations in the plasma. Small amounts of butorphanol can be detected in milk for as long as 36 hours following administration [18], suggesting that conservative withdrawal times for meat and milk would be 4 days 72 hours respectively.

Epidural Injection of Opioid Drugs - Dorsal horn neurons express opioid receptors. High concentrations of morphine can be delivered to dorsal horn cells by intradural or epidural injection, so consequently, epidurally delivered morphine can be beneficial for relief of in the perineum, posterior abdomen, or rear limb pain. Because of the infection risk, and potential for overdose, intradural injection is not commonly used in clinical practice. Perforation of the *dura mater* results in increased intrathecal drug uptake. Therefore, in order to prevent overdose, it is important to avoid puncturing the *dura mater* when delivering an epidural opioid dose. Dosages of morphine for epidural administration are at least 3 fold greater than those for intrathecal administration. Even if morphine is delivered epidurally, dural puncture increases the opioid concentration in the CSF by at least 8 fold over a pure epidural injection. If one were to puncture the *dura mater*, and deliver an epidural dosage of morphine, then the CSF concentrations of opiate could become dangerously high, and excessive CSF morphine could result in hypoventilation and hypoxemia [19]. Unlike epidural injections of xylazine, or mepivacaine, morphine does not paralyze motor nerves. The duration of activity of epidurally delivered morphine is thought to be approximately 12 hours in cattle. Because of the slow diffusion into the spinal cord, the peak activity following an epidural injection of morphine occurs between 210 and 250 minutes post-dosing. Concentrations ranging between 112 and 555 µg/ml in the CSF are greater than are achievable from systemic dosing. The high CSF concentrations can be sustained for at least 12 hours after a single injection. If possible, epidural morphine should be given to patients 2 to 3 hours prior to initiation of surgical procedures. Epidural morphine injection is also useful for the treatment of animals with painful conditions of the pelvic limbs.

Epidurally delivered morphine should be given at a dose of 0.1 mg/kg of body weight, twice daily. The drug treatment may be repeated as many times as is necessary. A preservative free product is commercially available for epidural administration to human beings, but the product is prohibitively expensive for use in livestock. We therefore administer the commercial parenteral formulation diluted to 10 to 20 ml in sterile saline solution. For relief of tail or perineal pain, morphine can be injected into the epidural space located between the second and third coccygeal vertebrae. For treatment of abdominal or pelvic limb pain, morphine should be injected into the space between the sixth lumbar and the first sacral vertebral bodies.

When performing an epidural injection at the lumbosacral space, the skin overlying the vertebral bodies should be locally anesthetized and incised. For adult cattle, a 6 inch, 18 gauge spinal needle should be inserted until the *ligamentum flavum* is pierced. Attach an air-filled glass ground syringe to the needle, and depress the plunger while advancing the needle. Rapid and easy emptying of the air occurs as the needle tip enters the epidural space. Once the epidural location has been confirmed, attach a morphine filled syringe aseptically to the hub of the needle and inject the drug rapidly.

Opioids with high lipid solubility diffuse more rapidly than opioids with polar characteristics. Therefore, buprenorphine could act more rapidly than morphine, but would dissipate more rapidly when injected extradurally. This would result in a shorter duration of activity for epidural buprenorphine than for epidural morphine [20].

### **Non-Steroidal Anti-inflammatory Drugs (NSAIDs)**

Classes of the non-steroidal anti-inflammatory drugs (NSAIDs) include the carboxylic acid compounds aspirin, flunixin, and carprofen, and the enolic acid compounds exemplified by phenylbutazone. The NSAIDs exert antipyretic, and anti-inflammatory activities through prostaglandin inhibition. Flunixin and possibly other NSAIDs, may also reduce pain through centrally mediated mechanisms involving  $\alpha_2$  and  $\mu$  opioid receptors [21]. The classical activity of NSAIDs, however, is to reduce arachidonate breakdown through inhibition of membrane bound cyclooxygenase. A large part of the anti-inflammatory effect of an NSAID therefore is to reduce the intracellular concentrations of thromboxane A<sub>2</sub>. The NSAIDs also reduce the formation of other inflammatory prostaglandins including PGE<sub>2</sub> and PGI<sub>2</sub>. The prostaglandins are not tissue irritants, but enhance pain and inflammation by inducing the liberation of histamine and bradykinin and mast cell components. The mechanisms for the centrally mediated effects of flunixin are unknown [22,23].

Cyclooxygenase (COX) that is released from damaged cell membranes synthesize proinflammatory prostaglandins. There are 2 COX isoenzymes designated as COX1 and COX2. COX 2 is an enzyme that occurs in most tissues. COX2 produces PGI and PGE which are sparing to the renal blood flow, and which participate in healing of gastric ulcers. The enzyme is constitutively produced in the renal cortex, and brain, but is inducible in other tissues. COX1 is a constitutive enzyme that synthesizes inflammatory related prostaglandins, especially E<sub>2</sub>, and mucosal and renal tubular protective prostaglandins. Initial studies suggested that COX2 specific NSAIDs may have fewer side effects while delivering an anti-inflammatory response of similar magnitude to that of the COX1 inhibitors. Subsequent research has shown that this may not be rigorously true. There appears to be a considerable overlap between the physiologic functions of the COX isoenzymes. Genetically altered COX2 deficient mice possess normal immunologic responses, but develop renal failure due to loss of a constitutively produced COX2 enzyme. Prostaglandins synthesized by COX2 are also involved in tissue regeneration, ovulation, and parturition. COX2 is also necessary for healing of preformed gastric ulcers. Therefore, selective inhibition of the COX2 isoenzyme may not be in the patient's best interest if gastric ulceration is imminent. Conversely, many inflammatory responses can be traced to the effects of COX1 induced eicosanoids. Because of the functional overlap between the 2 enzymes, and their collaborative activities in the inflammatory cascade, selective COX2 inhibitors may not be as efficacious or as safe as drugs that inhibit both isoenzymes.

Current drugs that are licensed for veterinary use inhibit COX to varying degrees. Strict classifications as either COX1 or 2 inhibitors may be inaccurate, because assays for COX selectivity are susceptible to error.

Certain NSAIDs also deliver analgesia through central inhibition of pain responses. Flunixin or dipyron increased pain thresholds in healthy sheep by 18 to 21% after 30 minutes for as long as 3 hours. The NSAID related analgesia was eliminated by pretreatment with either atipamezole or naloxone, indicating the importance of  $\mu$  and  $\alpha_2$  adrenergic receptors in the analgesic mechanisms of certain NSAIDs [24].

The anti-inflammatory effects of NSAIDs in ruminants consistently last longer than would be expected by examination of the concentration-time serum profiles. Prolonged therapeutic activities of the NSAIDs are probably due to extensive tissue binding and prolonged release. Orally administered NSAIDs are well absorbed in ruminants. Absorbed drugs are bound to plasma proteins, and possess a low volume of distribution ranging between 200 to 300 ml/kg. For excretion, NSAIDs are conjugated to glucuronic acid in the hepatic sinusoids, and are excreted through the bile and kidney as the inactive glucuronide. Phenylbutazone is converted to an active metabolite, oxfenbutazone by the liver, prior to conjugation. There is extensive enterohepatic recirculation of conjugated NSAIDs, and small amounts of NSAID may be excreted untransformed in the urine. Side effects of these drugs can be enhanced by simultaneous use of different classes of NSAIDs.

Renal papillary necrosis occurs in animals that have been overdosed with NSAIDs. This condition, which may be

irreversible in severe cases is thought to be related to an inhibition of (PG)E<sub>2</sub> in the renal medulla and (PG)I<sub>2</sub> in the renal cortex. Hypotension increases the potential for NSAID related papillary necrosis. Carprofen has a weak affinity for both COX enzymes, and hence has little effect upon renal perfusion in hypotensive patients. Activities and pharmacokinetic behaviors of specific NSAIDs in livestock are discussed below.

Flunixin meglumine - Flunixin meglumine is a potent carboxylic acid NSAID. Flunixin effectively inhibits COX1, and blocks eicosanoid mediators (TX)A<sub>2</sub> and (PG)E<sub>2</sub>. When administered intravenously at a dose of 1.1 mg/kg of body weight, the elimination half-life of flunixin ranges between 148 and 229 minutes. The total body clearance rate is 2.51 ml/kg/min, the volume of distribution is 0.397 L/kg, and the recommended dose ranges between 1.1 mg/kg 3 times daily, and 2.2 mg/kg of body weight, administered twice daily [25-27]. In our clinic, we prefer to use 1.1 mg/kg, 2 to 3 times daily intravenously.

Flunixin is considered to be an effective analgesic, but research trials have shown variable effects upon pain responses in food animals. In one study, sheep with foot rot had no analgesia after a single flunixin treatment. Sheep that were treated with flunixin for 3 serial days had a small but significant reduction of the mechanical stimulation threshold [28]. This study had numerous flaws including the use of sheep that were bilaterally and biaxially affected with foot rot, and by the breed heterogeneity of the subjects. The authors concluded that the presence of foot rot in 2 forelimbs would have artifactually increased the threshold because the sheep would have been unwilling to lift the stimulated leg. A different study showed that the drug had analgesic properties in both healthy and lame sheep [24]. The recommended drug withdrawal time for flunixin meglumine for meat is 10 days, and that for milk is 72 hours. Because of the potential for myonecrosis and injection site inflammation, flunixin should be administered intravenously [30].

Aspirin - Aspirin is not approved for use in food animals by the United States Food and Drug Administration, and therefore, has no acceptable residual carcass level. Nevertheless, the drug is administered to food animals at a dose of 100 mg/kg of body weight orally, twice daily [31]. At that dosage, therapeutic concentrations of salicylate (30 µg/ml) would be maintained in plasma. The elimination half-time for aspirin is 3.70 hours, and the volume of distribution is 0.24 L/kg. The biologic half-life after oral administration is 0.54 hours. The Food Animal Residue Avoidance Databank recommends that aspirin treated animals be given withdrawal time of 24 hours for both meat and milk.

Phenylbutazone - Phenylbutazone has been used for the treatment of downer cows. Failure to observe prolonged withholding time in phenylbutazone treated downer cows has resulted in extensive carcass adulteration, and condemnation. Residue avoidance of phenylbutazone is difficult because absorption and excretion of phenylbutazone is related to breed, age, species and diet, and withdrawal times are unpredictable [32,33]. Given this and the high level of regulatory concern about the drug, we do not recommend the use of phenylbutazone in any livestock species. The Food and Drug Administration has banned the administration of phenylbutazone to dairy animals, and strongly recommends against using the drug in any food producing animal.

Plasma phenylbutazone is extensively protein bound, and in ruminants, has a prolonged half-life ranging between 30 and 80 hours. When administered to cattle at doses of 24 mg/kg of body weight initially, and then 12 mg/kg every 24 hours, the drug was detectable in milk for as long as 82 hours [33,34]. Given the lack of a predictable withdrawal time, and the heightened concern shown by the regulatory agencies, one should preclude the clinical use of phenylbutazone in any species of food producing animals [35].

Ketoprofen - Ketoprofen inhibits cyclooxygenase, and lipoxygenase, but it is not approved by the Food and Drug Administration for administration to food producing animals. The anti-inflammatory activities of the drug include inhibition of β glucuronidase, prostaglandin E<sub>2</sub>, and thromboxane B<sub>2</sub>. The drug does not inhibit the synthesis of leukotriene B<sub>4</sub> [36]. The short plasma half-life (30 minutes), and low volume of distribution (0.2 L/kg) suggest that the drug could be used safely in dairy cattle, with minimal risk for carcass or milk adulteration. At peak blood levels, the milk concentrations of the drug are less than the test sensitivity, indicating that the required milk withdrawal time is short, and predictable. Withdrawal time for meat is recommended to be between 4 and 7 days. Providing the criteria for extra label drug use can be met, ketoprofen can be administered to food producing animals once daily at a dosage of 3.3 mg/kg of body weight [37]. Oral administration of ketoprofen (3.0 mg/kg of body weight) to 4 to 8 week old calves prior to, and then 2 and 7 hours after hot iron dehorning resulted in reduced pain-related behaviors [38]. Currently, oral forms of ketoprofen are not available in the United States.

Carprofen - Carprofen is a newer NSAID that possesses a weak antiprostaglandin activity and has a lower potential for ulcerogenicity than most other NSAIDs. Carprofen has a single chiral center and isomeric enantiomers with differing biological potencies. The mode of action of carprofen is unclear, because the effects of the drug on both COX1 And COX2

enzymes are poor compared to other NSAIDs. The reduced anti-COX1 activity is probably the reason for its reduced ulcerogenicity compared to other NSAIDs. The potency of carprofen is similar to that of indomethacin, but greater than that of phenylbutazone and aspirin [39].

When administered intravenously to sheep at doses of either 0.7 and 4.0 mg/kg of body weight, carprofen has volume of distribution of 0.095 and 0.118 L/kg of body weight and respective elimination half-lives of 26.1 and 33.7 hours. For both dosage rates, the body clearance rate was 2.5 ml/kg/hour. Plasma concentrations of carprofen  $\geq 1.5$   $\mu\text{g/ml}$  are analgesic. After administration (4.0 mg/kg of body weight intravenously), therapeutic plasma concentrations of carprofen are maintained for at least 72 hours. Measurable amounts of the carprofen are detectable in the milk of mastitic cattle that were given a single intravenous dose of 0.7 mg/kg of body weight [40-42]. Because of the prolonged clearance times, detectable milk distribution, and high peak plasma concentrations, carprofen should not be used in food producing animals until suitable voluntary withholding times are established.

### **$\alpha_2$ Adrenergic Agonists**

The dorsal horn neurons of the ruminant spinal cord are richly endowed with  $\alpha_2$  adrenergic receptors which bind to systemic or epidurally delivered agonists or blockers. Agonists for these receptors are analgesic. Activated receptors initiate the release of norepinephrine from pre- or postsynaptic neurons. There are 4 functional isotypes of  $\alpha_2$  adrenergic receptors. Type I receptors are located on the presynaptic noradrenergic nerve terminal, and prevent norepinephrine release from the postsynaptic neurons. Type II receptors inhibit the release of serotonin, dopamine and acetylcholine from presynaptic neurons. Type III receptors are located on postsynaptic neurons and belong to the G protein linked receptor super family. Type IV receptors are epinephrine responsive and are distributed on neurons throughout the CNS. The  $\alpha_2$  adrenergic receptors are also located on non-neural tissues including adrenal cortex, pancreas, and platelets [43].

Central depression due to  $\alpha_2$  activity is unrelated to peripheral noradrenergic activities [43-45], and is greater than can be explained by disruption of noradrenergic pathways alone, The sedation is apparently related to the activity of a stereospecific (D-) enantiomer on  $\alpha_2$  post-synaptic receptors.

Parenteral Xylazine - In the USA, the common  $\alpha_2$  adrenergic agonists for livestock include xylazine and detomidine. Xylazine has been recommended for systemic administration at doses ranging between 0.1 and 0.3 mg/kg of body weight. When given at a dose of 0.2 mg/kg of body weight, the body clearance was 42 ml/kg/min and the volume of distribution was 1.944 L/kg. The time of analgesia is approximately 30 minutes, but sedation may last as long as 36 hours [46,47]. Following intravenous injection to cattle or sheep, the respective pharmacologic half-lives of xylazine is 36.5 and 23 hours, and the half-life of detomidine in calves is 1.32 hours. The recommended withdrawal time for milk of xylazine is 72 hours. Drug concentrations of xylazine in milk are  $<0.4$  ppb by 11 hours post-dosing, and become undetectable by 24 hours post-dosing. When administered parenterally at a dose of 50  $\mu\text{g/kg}$ , xylazine is anti-nociceptive to both thermal and pressure stimuli for as long as 45 minutes [46]. Analgesia occurs in minutes after intravenous injection. Xylazine induces characteristic cardiovascular changes that include bradycardia, hypertension followed by hypotension, decreased pulmonary blood flow, reduced  $\text{PaO}_2$ , and increased blood  $\text{PaCO}_2$ .

Epidural Xylazine - Xylazine can be administered epidurally at doses ranging between 0.05 and 0.07 mg/kg of body weight in 5 ml total volume for control of pain in cattle. Xylazine treated cattle become recumbent by 30 minutes post-dosing [48]. Concomitant sedation of calves with 0.1 mg/kg xylazine combined with 0.18 to 0.24 mg/kg lidocaine and 0.05 mg/kg xylazine delivered in the lumbosacral epidural space (between vertebrae L5 and L6) also provides partial anesthesia and immobilization for umbilical hernia surgery in neonatal male dairy calves [49]. Epidural administration of xylazine (0.3 mg/kg of body weight) in sheep produced a near surgical plane of anesthesia on the ventrum and rear limbs, however, sheep that were treated in that manner developed a hypoxemia, and metabolic alkalosis [50].

Epidural xylazine apparently has no real advantage over local injections of an amide type local anesthetic solution combined with systemic xylazine sedation [51,52]. Moreover, in our clinic, 3 cows given epidural xylazine have been irreversibly paralyzed. Necropsy of the recumbent cows showed marked demyelination of the lumbar spinal cord segments. One calf in our clinic also developed a near fatal apnea immediately after receiving an epidural injection of xylazine. Whether this reflects a reaction to the preservative in the xylazine, or to the drug itself is unclear. We suspect that xylazine analgesia induced by intradural or intrathecal injection may in part, be due to demyelination. For that reason, spinal, epidural or intrathecal injection of xylazine cannot be recommended for implementation in clinical food animal practice. For epidural anesthesia, our clinic recommends the use of a 4 to 5 ml dose of 2% lidocaine in cattle and a 1 to 2 ml dose in sheep [51].

The recommended voluntary withdrawal time for xylazine in meat producing animals is 72 hours. The Food and Drug Administration is concerned about the use of xylazine in food producing animals, because a major metabolite of xylazine, 2,6 dimethylaniline, is carcinogenic [53]. At this time, there is no evidence that xylazine at tranquilizing doses has carcinogenic potential for livestock.

The effects of xylazine can be reversed by slow intravenous injection of tolazoline, which has been approved for use in food animals by the United States Food and Drug Administration. Tolazoline enters the central nervous system rapidly after intravenous injection. When reversing the effects of xylazine in fractious animals, the drug should be administered through a non-anchored jugular vein catheter and several intravenous extension lines. This arrangement allows the treatment personnel to remain separated safely from the recovering patient. The voluntary withholding time for meat in tolazoline treated animals is 30 days. Atipamezole, another  $\alpha_2$  receptor antagonist is not approved for use in food producing animals, and therefore, cannot be substituted for tolazoline.

**Detomidine** - Detomidine is an  $\alpha_2$  receptor agonist, which has similar *in vivo* effects as xylazine. In contrast to xylazine, detomidine treated animals usually remain standing after an intravenous dose. The drug's volume of distribution after a single intravenous dose of 0.08 mg/kg of body weight is 0.73 L/kg, and the elimination half-life is 1.32 hours. Although separate kinetics have been measured for intramuscular dose, we recommend that detomidine be administered intravenously under most clinical scenarios. The total body clearance is 12.3 ml/min/kg. The drug cannot be detected in milk 23 hours after a single intravenous dose [54].

Detomidine is currently used in our hospital at an intravenous dose of 0.01 mg/kg of body weight. The drug has been given epidurally to cattle, but we have had no experience with this form of treatment. Caudal epidural administration of medetomidine (5  $\mu$ g/kg of body weight in 5 ml total volume) produced analgesia within 5 minutes. The analgesia lasts for as long as 412 minutes. Transient recumbency of cattle may occur following epidural administration of detomidine [55].

<b>Recommended dosages routes intervals and withdrawal times of selected analgesic drugs in food animals.</b>					
<b>Drug</b>	<b>Route</b>	<b>Withdrawal Time</b>		<b>Dose (unit/kg of body weight)</b>	<b>Dose Frequency</b>
		<b>Milk (hours)</b>	<b>Meat (days)</b>		
Fentanyl	Transdermal	?	?	100 $\mu$ g patch per 60 kg	3 days
Morphine	Subcutaneous/Intravenous	0	0	0.05 to 10 mg	4 hours
Buprenorphine	Subcutaneous	0	0	0.005 to 0.01 mg	6 hours
Butorphanol	Subcutaneous/Intravenous	72	2	0.02 to 0.05 mg	4 hours
Flunixin	Intravenous/Oral	72	10	1.1 to 2.2 mg	6 to 12 hours
Aspirin	Oral	24	1	100 mg	12 hours
Ketoprofen	Intravenous	24	7	3.3 mg	24
Detomidine	Intravenous	72	7	0.05 to 0.08 mg	As needed
Xylazine	Intravenous/Subcutaneous	72	5	0.1 to 0.3 mg	As needed
Tolazoline	Intravenously (slowly)	NA	30	2 to 4	One time titrate from lower to higher dose

Note: Data are extracted from [35] and [56]

### **Specific indications for analgesics**

**Castration** - Optimal methods for pain control during castration are controversial. Castration related pain has been correlated with increased concentrations of plasma cortisol, and correlative behavioral changes that include statue standing, vacant staring, restlessness, and repeated recumbency. There is some disagreement relating to the various sampling protocols for plasma cortisol, and to the validity of behavioral assessments, however, it appears that experimental protocols requiring early and repeated measures are most accurate. Methods of castration include surgical emasculation, elastration (banding), and emasculatome neutering.

Use of epidural xylazine analgesia for castration of bulls has been investigated. A single dose of 0.07 mg/kg of xylazine was diluted in 7 ml of sterile saline solution and was injected into the epidural space between the first 2 coccygeal vertebrae. When administered in that fashion, most cattle remained standing, yet had significant reduction of intraoperative pain as measured by a reduction of avoidance behaviors. Clinicians in our veterinary hospital do not recommend the epidural administration of xylazine because the drug has demyelinated the spinal nerves of at least 2 cows [61].

All forms of castration induce abnormal pain related behavior, and increase the plasma cortisol concentration [57-60], regardless of the type of surgical procedure that is employed. Absolute pain control during castration can be provided by the combined technique of elastration (application of a rubber band) accompanied by intra-testicular administration of lidocaine at the time of band application. Additional analgesia can be obtained by timing the anesthetic injection to occur at least 15 minutes prior to the initiation of the surgery and by placing a portion of the anesthetic into the scrotal neck. If the testicles cannot be injected with lidocaine, clamping of the entire scrotal neck using an emasculator distal to a strangulating rubber ring decreases pain sensation to the level of that produced by combined elastration and intra-testicular lidocaine injection [62,63].

Other attempts at controlling castration associated pain by pharmacologic methods including epidural administration of morphine, or etorphine have been unsuccessful for relieving intra- or post-operative pain in lambs. Epidural morphine (8.0 mg), etorphine (5 nmol), or xylazine (25 µg) had little effect upon post-castration behavior [64].

In our veterinary clinic, we prefer surgical removal of the testis because the healing time is faster, the failure rate is lowest, and owners expect the method to be used for their animals. At the time of surgical removal, the testicles are anesthetized using intra-testicular lidocaine injection. For this procedure, an 18 gauge, 1.5 inch needle is inserted into the testicular parenchyma, and lidocaine is injected until it has filled the entire space. At that time, significant back-pressure is detected on the syringe plunger. A separate subcutaneous infusion of lidocaine is made in the distal third of the scrotum. Between 5 and 30 ml of 2% lidocaine is injected into the scrotums of small ruminants and calves respectively [63,65-67].

Dehorning and Disbudding - Considerable controversy exists over the ideal method for horn removal, and even over the validity of research methodologies that have been employed for quantifying dehorning related pain. Plasma measures of cortisol do not appear to reflect the actual pain modalities of animals during dehorning, and there is an unclear relationship between the degree of pain processed by the patient and the height of cortisol peak. Thermally disbudded calves develop lower blood cortisol spikes, and show fewer painful behavioral traits than scoop dehorned calves, suggesting that cauterly dehorning of younger calves is preferable to surgical dehorning at a later age. Even with thermal disbudding, there appears to be some disagreement about the necessity for regional anesthesia. For instance, in one study, plasma cortisol concentrations in thermally disbudded calves were no higher in calves that had been given regional anesthesia than in non-anesthetized controls. Despite this, locally anesthetized calves showed fewer escape attempts, and had fewer acute dehorning related pain responses than the nonanesthetized controls. Local anesthesia dissipates after several hours, and inevitable rises of plasma cortisol occur even when the local anesthesia is repeated [68]. Ancillary intravenous treatment of dehorned calves with ketoprofen may be useful for reducing the post-surgical plasma cortisol spikes, suggesting NSAIDS should be administered post-dehorning in cases where the owner is willing to pay for the additional costs [69].

For dehorning in our clinic, all animals receive regional anesthesia via a cornual nerve block. Lidocaine (2%) is used for all patients. Goats are also given regional anesthesia using infratrochlear, cornual, and ring nerve blocks, and are sedated with 0.1 mg/kg of xylazine intramuscularly. We do not dilute the lidocaine to a final 1% concentration when anesthetizing goats, but are careful to inject less than a dose that is equivalent to 10 mg/kg of the animals body weight [70]. Horns that are less than 1 cm in diameter at the base are removed by thermal cauterly, but horns that exceed 2 cm in diameter are surgically removed. After surgical removal, hemorrhage is controlled by pulling the corneal artery (calves), or by ligating it (goats). The edges of the surgical incisions are then burned using an electric dehorner. If the owner requests additional analgesia, the patients are given a single intravenous injection of flunixin meglumine (1 mg/kg of body weight intravenously).

The frontal sinus has penetrated the horn base in goats >8 months of age. Since dehorning in these patients opens the frontal sinus, a snug 4 layer bandage is applied for as long as 1 month. The material used for the bandage include a Telfa pad over the dehorning site, a sterile 1 inch Kling gauze roll figure eighted around the ears and the horn base, a 4 to 6 inch diameter stockinette, extending from the tip of the nose to the mid neck. Eye and ear holes are cut after the stockinette is in place. The 4th layer is composed of an elastikon wrap. Be sure that the wrap is not over-tight in order to avoid edema and postoperative pain.

Perineal Surgery, Injuries (Obstetrical, Rectal, Vaginal, Bladder) - Obstetrical pain can be severe, and analgesia should be administered if a patient vocalizes while undergoing obstetrical procedures. Epidural anesthesia provides some transient relief, but does not eliminate pain transmission from the cervix and anterior vagina. Administration of butorphanol (0.04 mg/kg of body weight intravenously) may reduce nociception during standing surgical procedures. For standing surgical procedures, administration of morphine (0.1 mg/kg of body weight diluted into 20 ml of sterile saline) into the epidural space between L6 and S1 vertebrae may have some benefit, although the analgesia produced by opioids is far less than that provided by an amide type of local anesthetic. Animals that are vocalizing, shifting weight, or are tachypneic, or are exhibiting severe distress should be sedated with detomidine (0.05 mg/kg of body weight, intravenously), or xylazine. Xylazine should be used with caution because it lowers systemic blood pressure, enhances tissue hypoxia, and could lower the overall survival rate in compromised animals [71].

Perineal or obstetrical pain in small ruminants may be eliminated for several hours by administration of a lumbosacral anesthetic. For administering the epidural anesthesia, the skin over the space between dorso-spinous processes of L6 and S1 vertebrae is surgically prepared and anesthetized using subcutaneous injection of 2% lidocaine. A longitudinal incision 0.5 cm in length is made, and a 3.5 inch, 19 gauge spinal needle is inserted through the *ligamentum flavum* and into the epidural space. Once the needle is in place air should inject easily. Replace the air filled syringe and, inject 1 ml per 7 kg of body weight of 0.75% bupivacaine. Paralysis of the rear legs should be immediate. Resuscitation may be required in patients that become apneic shortly after administration of the bupivacaine. Because of the risk for life-threatening injuries to the Achilles tendon, and extensor muscles of the rear limbs, spinal anesthesia of large ruminants and sheep weighing more than 75 kg is not recommended.

For longer term pain relief that may be needed for necrotic vaginitis, an alcohol epidural anesthetic might be considered. The technique is similar to a standard epidural injection between the first 2 coccygeal vertebrae. Lidocaine 2% is diluted 1:1 with 95% ethyl alcohol, and for cows, 2 to 3 ml are injected into the space between Cd1 and Cd2.

Digital or Limb Pain - Acute, short-term digital pain can be controlled by administration of an intravenous regional anesthesia. To administer the lidocaine, apply a tourniquet to the mid cannon bone, and disinfect the skin over the dorsal pedal vein. Inject 2% lidocaine into the vein. The respective lidocaine doses for cattle and small ruminants are 20 and 4 ml. For longer term pain control, 40 to 100 mg of morphine can be injected directly into the dorsal pedal vein, or into the affected synovial structure. Pelvic limb pain can be controlled using a lumbar epidural injection of morphine (0.1 mg/kg of body weight).

Intestinal or Peritoneal Pain (colic) - Control of pain emanating from the silent nociceptors of the bowel and abdomen may be difficult. Lumbosacral epidural administration of morphine may be helpful. Pain can be mitigated by concomitant administration of detomidine (0.1 mg/kg) intravenously, every 4 hours, and intravenous lidocaine. There is no basic data regarding the use of intravenous lidocaine for reduction of peritoneal pain, but the drug has been used in horses at a loading dose of 2% lidocaine (1.3 mg/kg), followed by an infusion of 1% lidocaine (0.05 mg/kg/min) [72].

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