U.S. Food and Drug Administration

Animal Health Literacy

Pain Measurement Techniques for Food-Producing Animals Could Lead to Pain Control Drugs

Pain relief in animals currently is a hot topic in veterinary medicine.

Companion animal medicine, in particular, is leading the way regarding patient pain management. Drug sponsors have realized the public's demand for pet analgesics, and, as a result, new non-steroidal anti-inflammatory drugs (NSAIDs) have been developed and approved for use in providing pain control for conditions such as osteoarthritis in dogs and postoperative pain and inflammation in dogs and cats.

In contrast, no drugs are approved for food animal analgesia in the United States. A major reason for the lack of approved food animal analgesics is that there are no validated methods for evaluating pain responses in food animals. For an analgesic to be FDA-approved, it has to undergo studies showing it is safe and effective. However, because no valid methods to measure food animal pain are available, the studies needed to show the analgesic actually controls pain are difficult to design.

Many groups around the world are working to identify and develop objective methods for measuring pain in cattle. Once these methods are developed

and validated, they can be used in the development and approval of safe and effective analgesic drugs for use during painful cattle husbandry practices and to control pain associated with various painful conditions commonly encountered in cattle management (for example, lameness).[1]

What is pain?

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” The IASP adds, “The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.” This is an important point—especially when discussing pain in animals, and even more so in food-producing animals, such as cattle. Animals can visibly communicate their pain to us only through physical signs; however, stoic animals, such as cattle in general, may have subtle signs that can be missed.

Many research groups around the world are attempting to solve the great mysteries of pain in both humans and other animals; how pain is transmitted, how it is processed, and how we control it.

Pain is a complex phenomenon. It involves many nerve cells, many types of nerve chemicals, and many different nerve cell receptors to which the nerve chemicals bind in order to continue a pain signal’s trip to the spinal cord and brain.[2]

Not only is pain complex from the standpoint of transmission, processing, and control, it is also complex in that there are different types of pain that have been identified based on cause or pathophysiology, the most important of which, for purposes of this discussion, are acute pain and chronic pain. Because the causes, transmission, and methods of processing of pain are complex issues, it is understandable that pain management and pain control are complicated and difficult.

Acute pain: Acute pain is a protective mechanism that can be defined as “the everyday experience of discomfort that occurs in response to a simple insult or injury.”[3] Acute pain makes us notice an injury, move away from the danger that caused the injury, and then take care of the injury; thus, it is generally short-lived pain. Pain associated with more severe trauma, like surgery, begins as acute pain but can become chronic with prolonged

inflammation.[4]

Chronic pain: Chronic pain is a persistent kind of pain that may or may not be associated with injury, but is generally associated with inflammation, changes to nerve cells, and hyperexcitability of the nerve cells in the spinal cord and brain.[5] This hyperexcitability phenomenon, or "wind up," is a physiologic increase in sensitization of excitable nerve cells. Because the brain and spinal cord are now wound up to detect pain, they are hypersensitive to future painful stimuli—thus, something normally mildly painful becomes very painful after repeated physical insults. (How many times have you consecutively banged your "funny bone" and found that each new hit was more painful than the last?) In addition, the wind-up phenomenon changes in the spinal cord and brain make pain resistant to treatment with analgesics.[6]

Prolonged inflammation caused by damaged tissue helps perpetuate the wind-up phenomenon and plays a large role in chronic pain.[7] Preventing the wind-up phenomenon is an important human pre-surgery consideration; studies have shown that if analgesic or anti-inflammatory drugs are given to a patient prior to surgery, less analgesic or anti-inflammatory drugs are needed to control pain after surgery.[8] So, preemptively controlling pain and inflammation associated with a surgery prior to the surgery itself may decrease the development of chronic pain. Additionally, use of surgical procedures that minimize inflammation may decrease the likelihood of chronic pain development.

Problems in detecting pain

Recognizing pain in cattle is an important step toward alleviating their pain and improving their wellbeing. Unfortunately, pain recognition in cattle is difficult due to their evolution as prey animals. Cattle (like other prey animals) learned to hide signs of pain and weakness in order to prevent becoming a predator's next meal. This self-preservation instinct, a help in the wild, can hinder veterinarians and producers trying to recognize and alleviate pain in their animals.

Signs commonly associated with pain in cattle include: vocalization (grunting or bellowing), abnormal standing posture, teeth grinding, tail swishing, changed facial expressions, decreased body weight or milk production, reluctance to move, decreased appetite, decreased grazing, kicking or stamping of feet, restlessness, head turning, limping, and

depression.[9 10 11]

In 2006, Huxley and Whay published an eye-opening article regarding cattle practitioners and their attitudes toward pain and use of pain drugs in cattle.[12] The authors sent a survey to nearly 2,400 cattle practitioners working in the UK and received 615 evaluable responses. Practitioners indicated that the most painful procedure for adult cattle was claw amputation and for calves was lower leg fracture repair and umbilical hernia repair. Surprising differences were found in assigned pain scores between women and men veterinarians and also among graduates from different decades: women and recent graduates generally gave higher scores, meaning higher levels of pain, for most conditions listed in the survey. Interestingly, although analgesics were widely used among practitioners, those who routinely used analgesics generally assigned higher pain scores to procedures than those who did not. Thus, the ability to recognize pain appears to drive the use of analgesics in practice. Based on the survey data, the authors recommended that current information regarding pain recognition and analgesic use in cattle be disseminated to UK cattle practitioners to ensure appropriate analgesia for cattle.[13]

In 2007, Dr. Hans Coetzee, BVSc, Ph.D., CertCHP, MRCVS, DACVCP, Assistant Professor of Clinical Pharmacology at Kansas State University College of Veterinary Medicine, and a group he organized conducted a small Web-based survey of U.S. bovine practitioners. Interestingly, only one in five respondents reported using analgesics at the time of castration. Why? The respondents stated they were concerned about using unapproved drugs in an extralabel manner in cattle due to requirements for careful calculation and observation of withdrawal times in treated animals. (Extralabel drug use refers to the use of a drug in a manner that is not in accordance with the approved labeling. Extralabel use of a drug can include use of the drug for indications, species, dosage levels, routes of administration, or withdrawal times not listed in the approved labeling.[14] A withdrawal time is the interval between the time of the last administration of a drug and the time when the treated animal can be safely slaughtered for food or its milk can be safely consumed.[15])

CVM's interest

Unlike the situation in small-animal medicine, there are no validated science-based pain assessment tools for use in cattle. This lack of validated pain

assessment tools provides a significant hurdle in the development of analgesics for cattle.

CVM's Guidance for Industry #123 ("Development of Target Animal Safety and Effectiveness Data to Support Approval of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) for Use in Animals") discusses development and approval of NSAIDs for animals and encourages the use of validated methods of pain assessment in the target species. CVM recognizes the current limitations of this recommendation with regard to food-producing animals and hopes that current research in food-producing animal analgesics, such as Dr. Coetzee's, will provide much needed, validated methods for evaluation of pain, thereby encouraging the development and approval of analgesics for food-producing animals.

During the May 2008 International Symposium on Beef Cattle Welfare, organized by Dr. Coetzee, CVM encouraged drug sponsors to meet with them and discuss their proposed development plans for new food-producing animal analgesics. Discussions with CVM will facilitate analgesic drug approval for food-producing animals within the confines of the regulations under which CVM functions.

Due to the issues surrounding pain control in animals, CVM's Staff College recently invited Dr. Coetzee to speak about the hurdles facing researchers and the animal drug industry regarding development of analgesics for food-producing animals, particularly cattle.

There are two main categories of pain assessment—subjective (which introduces some of the observer's bias in scoring) and objective (these methods rely on biomarkers of pain, such as bloodwork values, which have little or no observer bias and are generally quantifiable).

Use of "subjective" methods to obtain data for pain studies generally relies on observations and scoring of visible physical signs of pain exhibited by cattle. Validated subjective methods of pain assessment (such as the Glasgow Short Form Pain Questionnaire for dogs, which can be obtained at http://www.gla.ac.uk/faculties/vet/smallanimalhospital/ourservices/painmanagement andacupuncture) could be useful, particularly when they have clearly defined terms; however, none has been modified and validated for use in cattle. The observer's personal bias may still be introduced during scoring, thus, it is not uncommon to see differences in pain scores given by different observers for the same animal at the same time point.

Thus, researchers, including Dr. Coetzee, are trying to develop more objective tools for pain assessment. Examples of tools being evaluated by Dr. Coetzee's group include measurement of plasma Substance P values, evaluation of accelerometers, thermography, chute exit speed, and pressure mats.

Plasma Substance P: Substance P is a naturally occurring protein (neuropeptide) that plays roles in pain perception and transmission of nerve impulses, inflammation, regulation of various hormonal responses in the body, gastrointestinal movement, and vomiting.[16] Substance P helps regulate the excitability of the nerve cells associated with pain that are found in the dorsal horn of the spinal cord. Substance P is also involved in the integration of pain, stress, and anxiety.[17] Researchers have evaluated plasma Substance P levels in humans for varying conditions including osteoarthritis, headaches, and fibromyalgia.[18] They also found higher levels of plasma Substance P (27-times greater) in human patients with soft tissue injuries as compared to those from healthy control subjects.[19]

Based on these findings, Dr. Coetzee's group hypothesized that plasma Substance P response may be a more useful specific indicator of pain in cattle than plasma cortisol response. Cortisol is a hormone associated with the fight-or-flight system, and plasma levels of cortisol in animals are known to increase rapidly in the face of stressful but non-painful situations. Dr. Coetzee's group conducted a study evaluating plasma cortisol and plasma Substance P levels in 10 calves undergoing castration or simulated castration.[20] Average plasma cortisol concentrations in castrated calves were similar to those in uncastrated calves. Average plasma Substance P concentrations, however, were statistically significantly higher in castrated calves than those in uncastrated calves, lending support to their hypothesis. The group acknowledged that more research is necessary to distinguish how much of the plasma Substance P response after castration was due to stress from handling and how much was truly due to pain from the procedure. Overall, comparison of plasma Substance P and cortisol concentrations may provide a useful tool to help researchers, producers, and veterinarians distinguish pain from the stress of handling an animal for a given procedure.[21]

Accelerometers: Accelerometers are devices that can be used to measure an animal's movements in two or three dimensions. The devices are attached to an animal using leg bands. Behaviors such as standing, walking, grazing, or lying down, and the animal's posture can be recorded over a specified

period of time and then analyzed. An advantage to using these devices is that animals on study can be used as their own controls—that is, baseline pre-procedure behavior for a given animal can be compared with its post-procedure behavior—thus reducing unexplained variability.

Dr. Coetzee's group conducted an accelerometer study in 12 calves, comparing calf activity changes pre- and post-castration with those of calves in a control (non-castrated) group.[22] Dr. Coetzee's group found that castrated calves spent proportionately more time standing after castration (82.2 percent), compared with their pre-castration readings (46.2 percent).[23] Castrated calves also spent less time eating compared to both their pre-castration readings and those of the control calves. The group recorded the calves' behavior during the study on video cameras and was able to corroborate the accelerometer data with the behavioral observations. In the future, accelerometers may prove to be useful tools with which to assess pain behavior in cattle.

Thermography: Thermography may provide researchers with a safe, hands-off way to evaluate cattle pain during studies. Thermography is based on measuring changes in surface body temperature in response to painful stimuli. A specialized camera is placed in a specific location and a set distance from an animal confined in a squeeze chute. The camera can then detect changes in skin temperature associated with blood flow to the skin (white = hot, green/blue = cool). Pain is thought to increase the levels of circulating norepinephrine and epinephrine "fight-or-flight" hormones in the body. Because the chemicals cause blood vessels to constrict, blood flow to the skin is decreased and the skin's temperature then decreases. Skin temperature changes, noted by the camera as changes in skin color, can be recorded and quantified, providing another objective source of data for pain assessment. In addition to being a safe way to evaluate cattle, another advantage, like accelerometers, is that animals being evaluated by thermography can be used as their own controls: pre- and post-procedure images can be compared for an individual animal.

Dr. Coetzee acknowledges that more research is needed to confirm the validity of using thermography for pain evaluation. Other areas in thermography Dr. Coetzee would like to evaluate include: comparing different areas of the body (for example, head versus chest) to see which provides the best thermography results, ensuring that an animal's plasma epinephrine levels correspond to its recorded thermography changes, and evaluating

whether pain drugs would cause changes in thermography (less pain = less epinephrine = decreased skin temperature changes).[24]

Pressure Mats: Pressure mats, in addition to currently being evaluated in small animal medicine for pain evaluation, are also being evaluated for use in obtaining objective data for pain evaluation in cattle.[25] The mats contain built-in sensors that record pressure changes through all phases of an animal's stride. The data can be analyzed using special computer software to evaluate changes in duration and length of stride, force generated throughout a stride, the distribution of the force throughout a stride. The data give researchers a complete picture of how an animal is walking—how its weight is being distributed on each foot as it walks. The data are recorded as footprint images that vary in color depending on the amount of force an animal generates on each foot while walking (for example, red footprints mean the animal is putting a lot of pressure on those feet).

Dr. Coetzee's group has used video cameras to simultaneously record an animal as it walks across the pressure mats. The videos are then synchronized with the recorded pressure mat footfalls, giving the observers a way to score lameness for an animal subjectively (visual observations and scores) and objectively (numerical data points from pressure mats) at the same time. Again, this is a promising tool for use in future cattle pain studies.

Conclusion

Pain relief is a very hot topic in veterinary medicine. While there are currently no drugs specifically approved for analgesia in food-producing animals, there is growing interest in research in this area. The efforts of Dr. Coetzee and his fellow large-animal researchers around the world should ensure that pain measurement methods for food-producing animals are identified and that work toward the validation of these methods continues. Once validated pain measurement methods become available, they can then be used in the development and approval of much-needed analgesics for food-producing animals.

Endnotes

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