Pharmacokinetic – Pharmacodynamic Modeling of Analgesic Drugs in Beef Cattle

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Abstract

Bovine castration is performed on approximately 15 million cattle in the United States annually. Surgical castration with a scalpel followed by testicular removal using manual twisting (cattle < 90 kg) or an emasculator (cattle >90 kg) are the most common methods of castration performed in the USA. A survey of US veterinarians found that one in five practitioners report using analgesics or a local anesthetic at the time of castration. However, these drugs have not been formally approved by the FDA for pain relief. Validated methods of pain assessment are required in order to determine if analgesic drugs are efficacious. Potential pain assessment methods include plasma cortisol determination, plasma Substance P determination, accelerometers, thermography, chute exit speed, heart rate determination and electrodermal activity measurements. Studies have shown that a combination of butorphanol (0.01 - 0.025 mg/kg); xylazine (0.02 - 0.05 mg/kg) and ketamine (0.04 - 0.1 mg/kg) can mitigate these responses. Research is underway to further characterize the activity of analgesic drugs administered prior to castration.

Résumé

La castration bovine se fait sur approximativement 15 millions de bovins aux États-Unis chaque année. Les deux méthodes les plus couramment utilisées pour la castration aux États-Unis sont la castration chirurgicale avec scalpel suivie de l'ablation des testicules par torsion manuelle (bovins < 90 kg) ou par émasculateur (bovins > 90 kg). Une enquête auprès des vétérinaires américains indiquait qu'un praticien sur cinq utilisait des analgésiques ou un anesthésique local lors de la castration. Toutefois, ces drogues ne sont pas reconnues officiellement par le FDA pour le soulagement de la douleur. Des méthodes éprouvées d'évaluation de la douleur sont requises afin de déterminer si des drogues analgésiques sont efficaces. Des méthodes potentielles d'évaluation de la douleur incluent la mesure du cortisol plasmique, la mesure de la substance plasmique P, l'accéléromètrie, la thermographie, la vitesse de sortie d'une entrave, la mesure de la fréquence cardiaque et les mesures d'activité électrodermale. Des études ont démontré que la combinaison de butorphanol (0.01 - 0.025 mg/kg), de xylazine (0.02 - 0.05 mg/kg) et de kétamine (0.04 - 0.1 mg/kg) peut atténuer ces réactions. Des travaux sont en cours afin d'approfondir les mécanismes de l'effet analgésique des drogues administrées avant la castration.

Introduction

Nociception is an inevitable consequence of many routine management procedures in farm animals. Castration is considered one of the most stressful experiences for livestock by the American Veterinary Medical Association (AVMA)[1] and is performed on approximately 15 million calves in the US annually.[41] Dehorning and castration are especially significant in terms of animal welfare because preemptive analgesia can be applied in advance of the painful stimulus, thereby preventing sensitization of the nervous system to subsequent stimuli that could amplify pain. The AVMA "supports the use of procedures that reduce or eliminate the pain of dehorning and castrating of cattle"[2] and proposes that "available methods of minimizing pain and stress include application of local anesthesia and the administration of analgesics."[1] In spite of this, a recent survey of 184 bovine veterinarians conducted by our research group found that only one in five US veterinarians use anesthesia or analgesics at the time of castration. One reason for this discrepancy is the lack of objective methodology to quantify the most effective pain mitigation strategies.

It is remarkable that, although administration of local anesthesia prior to castration and dehorning is legislated in several European countries, there are currently no analgesic drugs specifically approved for pain relief in livestock by the US Food and Drug Administration (FDA). [2,8,12,37] FDA Guidance Document 123 for the development of effectiveness data for non-steroidal anti-inflammatory drugs (NSAIDs) states that "validated methods of pain assessment must be used in order for a drug to be indicated for pain relief in the target species."[42] The identification and validation of robust, repeatable pain measurements is therefore fundamental for the development and approval of effective analgesic drug regimens for use in livestock. Research to address our limited knowledge in this area is therefore essential to formulating science-based recommendations.

In practical terms, resistance to requiring injectable analgesia for routine castration and dehorning is largely based on time and logistical issues. However, a recent study evaluating novel methods of analgesia for tail docking in lambs demonstrated that castrating by banding in one to two-day old lambs required an average of 28 seconds without analgesia and 68 seconds when an injectable local anesthetic was administered by jet-injector. [20] While the United States has not followed other countries in legislating the use of local anesthesia during castration and dehorning, it is appropriate for the veterinary profession to pursue practical, rapid, and effective methods for the relief of pain related to these procedures. The authors are aware of practicing veterinarians that have adopted local anesthesia regimens for these procedures.

Results of a Survey of Current Methods of Dehorning and Castration in the USA

In a web-based survey, members of the American Association of Bovine Practitioners (AABP) and Academy of Veterinary Consultants (AVC) were asked to provide information about castration methods, adverse events and husbandry procedures conducted at the time of castration. Invitations to participate in the survey were sent to email addresses belonging to 1,669 AABP members and 303 AVC members. After partially completed surveys and missing data were omitted, 189 responses were included in the analysis. Surgical castration with a scalpel followed by testicular removal using manual twisting (cattle < 198 lb [90 kg]) or an emasculator (cattle >198 lb [90 kg]) were the most common methods of castration. The potential risk of injury to the operator, size of the animal, handling facilities and experience with the technique were the most important considerations used to determine the castration method. Swelling, stiffness and increased lying time were the most prevalent adverse events observed following castration. One in five practitioners reported using an analgesic or local anesthetic at the time of castration. Approximately 90% of respondents said they also vaccinate and dehorn cattle at the time of castration. Equipment disinfection, prophylactic antimicrobials and tetanus toxoid are commonly used to minimize complications following castration. The results of this survey provide insight into current bovine castration and management practices in the US.

Candidate Methods to Assess Pain Associated with Castration

The literature pertaining to behavioral response associated with castration has been summarized in an excellent review by Stafford and Mellor.[38] The salient points pertaining to this discussion are summarized below.

Behavior

Assessment of individual animal behavioral changes in response to pain is highly subjective. Escape behaviors demonstrated at castration but not seen afterwards may reflect a pain response[29] or a desire to escape confinement.[5,38] Studies have reported that surgically castrated calves struggle and kick during the operation but calves castrated with rubber rings are quieter.[15] Macauley and others[28] reported that calves castrated surgically moved around much less than control calves or calves castrated using a Burdizzo. Two days following castration, the surgical and Burdizzo castrated calves were observed to be less active than control calves. Robertson and others[35] found that rubber-ring, Burdizzo and surgical castration caused significant behavioral responses indicative of pain during the first three hours after castration. Fisher and others[17] reported that 14-month-old bulls castrated surgically stamped their hind feet, swished their tails and grazed less in the afternoon following castration than control bulls and bulls castrated using bands. Behaviors indicative of a painful sensation such as turning the head towards the hindquarters, alternate lifting of the hindlegs, abnormal postures and slow movement of the tail have been reported weeks after rubber-ring castration.[31] The relative level of pain associated with behaviors seen after castration has not been quantified.[18] The characteristics of emotional states, such as being fearful, anxious or happy, and other subjective states, such as pain sensation and perception, are such that they can never be precisely and accurately measured.[25]

Production Parameters

Production parameters are often too imprecise to reflect the pain experienced by animals following castration. Furthermore, weight gain following castration may be negatively influenced by a decrease in testosterone following removal of the testes.[24] However, assessment of production parameters is critical if animal well-being research is to have relevance to livestock producers. These assessments may take the form of a cost-benefit analysis or a measure of animal performance. In some studies, Burdizzo or surgical castration had no effect on average daily gain (ADG) over a three-month period following castration.[11,23] The ADG of seven-week-old calves during the five weeks following castration using rubber rings, clamp or surgery have been reported to be lower than non-castrated calves but similar between the different castration methods. Rubber ring and surgical castration were reported to cause a decrease in ADG of 50% and 70%, respectively, in cattle aged eight to nine months.[44] When eight, nine and 14-month-old cattle were castrated surgically or using latex bands, cattle castrated later had poorer growth rates than those castrated at weaning. Cattle castrated with latex bands also had lower growth rates than those castrated surgically during the following four to eight weeks.[17,24] In a study conducted by Oklahoma State University, 162 bull calves were used to determine the effects of latex banding of the scrotum or surgical castration on growth rate. Bulls that were banded at weaning gained less weight than bulls that were banded or surgically castrated at two to three months of age.[27] In a second study, 368 bull calves were used in two separate experiments to examine the effect of method of castration on receiving health and performance. In the first experiment, latex banding intact males shortly after arrival was found to decrease daily gain by 19% compared with purchasing steers, and by 14.9% compared with surgically castrating intact males shortly after arrival. In the second experiment, purchased, castrated males gained 0.58 lb more and consumed 1.26 lb more feed per day than intact males surgically castrated shortly after arrival.[4]

Cortisol Response

Several studies have evaluated acute cortisol response as a method to determine the extent and duration of distress associated with castration in cattle.[7,14,17,18,39] Studies reviewed by Stafford and Mellor[38] indicate that surgical and latex band castrations, especially when performed in older cattle, appear to elicit higher plasma cortisol responses that remain above pre-treatment levels for longer. Peak cortisol concentration following surgical castration occurs within the first 30 minutes after castration and ranges from 45 nmol/L following rubber ring castration to 129 nmol/L following surgical castration. The duration of plasma cortisol response above pre-treatment levels typically ranges from 60 minutes following Burdizzo castration to 180 minutes following surgical castration.[38] Fisher and others[19] reported that plasma cortisol response was significantly reduced during the first 90 minutes following surgical or Burdizzo castration in calves when the lidocaine was administered prior to the procedure. Lidocaine is a commonly used local anesthesia that has a fast onset of action of 10-15 minutes, and an intermediate duration of action of 60–120 minutes.[26,36] Based on these data, increases in plasma cortisol are believed to reflect pain experienced as a result of castration.[37]

Cortisol has been widely used as a measurement of distress since its response magnitude, as indicated by peak height, response duration and/or integrated response usually accords with the predicted noxiousness of different procedures.[29] At each end of the cortisol response range, however, interpretation is less straightforward. At the lower end, for example, studies have shown that tail docking with a ring and tail docking with a docking iron cause similar cortisol responses to control handling in older lambs.[32] At the upper end of the range, there are several examples where cortisol responses do not increase proportionally to the severity of different treatments as might be expected. This may suggest a "ceiling effect" on plasma cortisol responses.[9,32] Other studies have shown that plasma cortisol concentrations following surgical castrations vary greatly between animals.[39] Based on these data, it has been hypothesized that low responses may be due to individuals having high pain thresholds.[38] Variations may also come about due to differences in the way in which a particular castration method is performed by different operators. These data suggest that plasma cortisol levels may not always accurately reflect the extent of the pain response in animals.

Substance P

Substance P is an 11-amino acid prototypic neuropeptide that regulates the excitability of dorsal horn nocireceptive neurons and is present in areas of the neuroaxis involved in the integration of pain, stress, and anxiety. Studies have shown that plasma SP levels are up to 27-fold greater in human patients with soft-tissue injury than healthy controls.[33] Our research group recently conducted a study to evaluate plasma substance P (SP) and cortisol response following castration.[10] Calves were acclimated for five days prior to random assignment based on scrotal circumference to a castration or uncastrated control group. Blood samples were collected at -24, -12, and 0 hours pre-castration and 3, 10, 20, 30, 45, 60, 90, 120, 150, 180, and 240 minutes post-castration. Vocalization and attitude scores were determined at the time of castration or simulated castration. Plasma SP and cortisol were determined using competitive and chemiluminescent enzyme immunoassay, respectively. Data were analyzed by repeated measures analysis using a Mixed Effects model allowing for unequal variances. No significant difference in plasma cortisol response between castrated and uncastrated calves was observed over time (p=0.644). In contrast, mean plasma SP concentrations were significantly higher in castrated calves compared to uncastrated controls over the course of the study (p=0.042). Cortisol responses over time in calves with vocalization scores of 0 were not significantly different from calves with vocalization scores of 3 (p=0.17). However, calves with vocalization scores of 3 had significantly higher SP levels when compared to calves with scores of 0 (p=0.033). These findings contradict previous reports that show an increase in plasma cortisol relative to pain post-castration. Significant increases in plasma SP concentration post-castration suggest that this measurement may be associated with nociception; however, further investigation is necessary.

Accelerometers

Accelerometers have been used in other species to detect lameness[22] and remotely monitor level of animal activity. [21] Our research group has utilized video observations to determine the accuracy of accelerometers to measure behavior changes in cattle and to determine differences in beef bull behavior post-castration. [43] Three Holstein calves and 12 healthy beef bulls had two-dimensional accelerometers placed on three animals and data was logged simultaneous to video recording of animal behavior. The subsequent data set was used to generate and validate a predictive model to classify animal posture (standing or lying) and type of activity (standing in place, walking, eating, getting up, lying awake, or lying sleeping). The algorithms developed were used to conduct a prospective trial to determine differences in bull behavior in the first 24 hours post-castration (N=6) compared to both control animals (non-castrated) (N=6) and pre-castration readings from the same bulls. Based on the analysis of the 2-D accelerometer signal, posture can be classified with a high degree of accuracy (98.3%) and the specific activity can be estimated with a reasonably low misclassification rate (23.5%). Employing the system to compare behavior post-castration revealed that castrated calves spent a larger ($P < 0.05$) amount of time standing (79.3%) compared to either pre-castration readings (51.2%) or control calves after castration (64.3%). Animals also spent a lower percentage of the time eating in the post-castration phase. The 2-D accelerometers provided accurate classification of animal posture and reasonable classification of animal activity. Collected data allowed quantification of behavioral differences between animals after a surgical procedure and provides a valuable tool to compare research with behavioral endpoints.

Pharmacokinetic/ Pharmacodynamic Modeling of Analgesic Drugs

It has been suggested that a surgical stimulus such as castration in calves is so brief that little difference can be observed or measured between animals having or not having local anesthetic applied.[3] However, alleviating pain associated with surgical castration by administration of local anesthesia increased weight gain in cattle for 35 days following castration.[19] This suggests that alleviating acute pain at the time of castration may have economic benefit.[38] Ketoprofen, a NSAID analgesic not approved for use in cattle in the US, has been shown to reduce acute plasma cortisol response in cattle following administration at the time of castration.[14,39,40] Giving both a local anesthetic and intravenous ketoprofen before surgery-cut castration was found to virtually abolish the post-surgery cortisol response.[39,40] Ketoprofen given alone was also found to reduce the plasma cortisol response to Burdizzo castration more effectively than a local anesthetic or an epidural.[40] Similar studies examining NSAIDs that are approved for use in food-producing animals in the USA have not been conducted. Furthermore, all these studies examining the efficacy of analgesic drugs in farm animals fail to report associated plasma drug concentrations essential for designing efficacious analgesic regimens.

Some of the parameters described above may be useful to allow us to determine the efficacy of analgesics in food animals.

Our research group recently conducted a study to examine the effect of oral aspirin and intravenous sodium salicylate on acute plasma cortisol response following surgical castration.[9] Twenty bulls, randomly assigned to the following groups: 1) uncastrated, untreated controls; 2) castrated, untreated controls; 3) 50mg/kg sodium salicylate IV pre-castration; and 4) 50mg/kg aspirin (acetylsalicylic acid) per os pre-castration, were blood sampled at 3, 10, 20, 30, 40, 50 minutes and 1, 1.5, 2, 4, 6, 8, 10 and 12 hours post-castration. Samples were analyzed by competitive chemiluminescent immunoassay and fluorescence polarization immunoassay for cortisol and salicylate, respectively. Data were analyzed using noncompartmental analysis, a simple cosine model, ANOVA and t-tests. Intravenous salicylate Vd_{ss} was 0.18 L/kg, Cl_B was 3.36 mL/min/kg and $T_{½\lambda}$ was 0.63 hours. Plasma salicylate concentrations above 25 µg/mL coincided with significant attenuation in peak cortisol concentrations ($p=0.029$). Peak salicylate concentration following oral aspirin administration was less than 10 µg/mL and failed to attenuate cortisol response. Once salicylate concentrations decreased below 5 µg/mL, cortisol response in the castrated groups was significantly higher than uncastrated controls ($p=0.018$). To our knowledge, this is the first study relating plasma analgesic drug concentrations directly to mitigation of plasma cortisol response post-castration. These findings have important implications for designing effective analgesic regimens to alleviate the stress response associated with painful routine animal husbandry procedures.

A protocol for use of IM butorphanol/xylazine/ketamine (BXK) was presented by Dr. Matt Miesner, with credit given to Dr. Eric Abrahamsen, at the 2007 Kansas State University June Conference.[30] The regimen consists of butorphanol (0.01 – 0.025 mg/kg) + xylazine (0.02 – 0.05 mg/kg) + ketamine (0.04 – 0.1 mg/kg). Dr. Miesner noted that for a 990 lb (450 kg) animal, 5 mg butorphanol, 10 mg xylazine, and 20 mg ketamine would constitute the low end of the dosing range. Note that the calculation should involve 2X xylazine as compared to butorphanol and 2X ketamine as compared with xylazine. They have noted up to an hour of cooperation using this protocol, but more fractious patients may require increased doses. Dr. Miesner suggests giving no more than 10 mg butorphanol or 20 mg of xylazine as the initial dose (this would be for the 990 lb animal on up). The following withdrawal times are recommended by FARAD.[13]

- Ketamine, up to 2 mg/kg IV, up to 10 mg/kg IM, 3 days meat, 48 hours milk
- Xylazine, 0.016 – 0.1 mg/kg IV, 0.05-0.3 mg/kg IM, 5 days meat, 72 hours milk
- Xylazine, 0.3 – 2.0 mg/kg IM, 10 days meat, 120 hours milk.

A reasonable withdrawal time for opiates in cattle of at least 48 hours has been suggested in the literature.[34]

This regimen was evaluated in a study using 22 male beef cattle that were randomly assigned to one of four treatment groups: 1) uncastrated, untreated control (n=4); 2) castrated, placebo-treated control (n=6); 3) castrated, IV xylazine (0.05 mg/ kg) and ketamine (0.1 mg/kg) (n=6); 4) castrated, intravenous xylazine (0.05 mg/ kg) (n=6). Calves were castrated with a Henderson castration tool and blood samples were collected at 3, 10, 20, 30, 40 and 50 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 hours thereafter. Ketamine, norketamine and xylazine were determined by LC-MS-MS and substance P (SP) and cortisol were determined by use of competitive and chemiluminescent enzyme immunoassays, respectively. The volume of the central compartment (V_c = 132.82 ± 68.23 mL/kg), distribution clearance (CL_D = 15.49 ± 2.56 mL/min/kg), volume of the peripheral compartment (V_T = 257.05 ± 41.65 mL/kg) and ketamine clearance by the formation of the norketamine metabolite (CL_{2M} = 8.56 ± 7.37 mL/kg/min) were estimated. Plasma ketamine, norketamine and xylaxine concentrations were associated with mitigation of plasma cortisol and SP response.

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