PEER REVIEWED

Case series: Surgical treatment of non-responding diphtheria cases in feedlot cattle via long term tracheostomy

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Abstract

Laryngeal diphtheria is a contributor to morbidity and mortality in feedlot cattle. Medical treatment has resulted in great success; however, advanced cases often do not successfully respond to systemic antimicrobials. The purpose of this report is to describe a surgical procedure performed in field settings on feedlot calves with diphtheria that failed to respond to medical treatment. Forty-five medically non-responding clinical diphtheria cases were selected for surgery. The calves were restrained in a chute, surgically prepped, and local anesthesia was administered. A surgical incision through the skin, subcutaneous tissues, and a transverse incision between tracheal rings was performed. A tracheostomy tube was placed inside the tracheal incision to provide a patent airway. A total of 42 surgical cases (93%) with diphtheria completed the balance of the feeding period to harvest. Complications including obstruction due to organic material and loss of tube were managed successfully when identified early. Surgical treatment of calves failing to respond to medical therapy in feedlot cattle provides a practical option to perform in field settings with minimal risk for complications. While the incidence of non-responding diphtheria cases is small, surgical treatment of calves failing to respond to medical therapy provides an option to impact mortality of the affected population and allow preservation of resources.

Key words: bovine, diphtheria, feedlot, surgery

Résumé

La diphtérie laryngée contribue à la morbidité et à la mortalité chez les bovins de parc d'engraissement. Le traitement médical a connu beaucoup de succès mais les cas avancés ne répondent pas toujours bien aux antimicrobiens systémiques. Le but de ce rapport est de décrire une procédure chirurgicale sur le terrain impliquant des veaux de parc d'engraissement avec une diphtérie qui ne répond pas au traitement médical. Un total de 45 cas de diphtérie clinique ne répondant pas au traitement médical ont été choisis pour la chirurgie. Les veaux étaient retenus dans une entrave, préparés pour la chirurgie et recevaient une anesthésie locale. Une incision chirurgicale à travers la peau et les tissus sous-cutanés et une incision transversale entre les anneaux trachéens ont été faites. Un tube de trachéostomie a été placé à l'intérieur de l'incision trachéale pour établir une voie respiratoire. Un total de 42 cas (93%) avec diphtérie ont réussi à poursuivre l'engraissement jusqu'à la fin. Les complications, incluant l'obstruction causée par du matériel organique et la perte du tube, ont été réglées avec succès lorsqu'elles étaient identifiées tôt. Le traitement chirurgical des veaux de parc d'engraissement qui ne répondent pas au traitement médical représente une option pratique faisable sur le terrain et qui présente des risques minimes de complication. Bien que le nombre de cas de diphtérie ne répondant pas au traitement soit peu élevé, la chirurgie chez les veaux suite à l'échec du traitement médical est une option qui peut avoir un impact sur la mortalité dans les populations affectées et qui permet de sauvegarder des ressources.

Introduction

Laryngeal diphtheria, also known as necrotic laryngitis, is a contributor to morbidity and mortality rates in feedlot cattle. The incidence of laryngeal diphtheria in feedlot cattle in the United States has been estimated to be 1 to 2%.[6] *Fusobacterium necrophorum* and *Trueperella (Arcanobacterium) pyogenes* are the primary bacterial etiological agents associated with diphtheria cases in cattle.[7,9,11] Medical treatment of clinically affected calves has resulted in high success;

however, advanced cases often do not successfully respond to systemic antimicrobials commonly used for treatment.[2]

Surgical procedures with resection of the infected necrotic tissues have been suggested for cases which do not respond to systemic antimicrobials.[2,3,4,5,8,10,12] Previous studies evaluated surgical procedures performed under general anesthesia or in veterinary hospital situations with positive treatment outcomes.[3,4,12] However, to the authors' knowledge, there have been no studies evaluating surgical procedures performed in the field.

The purpose of this report is to describe a prospective study design of a surgical procedure performed in field settings during the course of providing normal veterinary services to privately owned feedlot calves with medically non-responding cases of diphtheria. The surgical approach was developed by duplicating the techniques commonly used to place tracheostomy tubes in other species, and experimenting on bovine cadavers. Evaluation of these outcomes may help identify additional management protocols to implement in feedlot situations to change outcomes of chronic diphtheria cases.

Materials and Methods

Clinical signs and cases identified

Feedlot personnel diagnosed diphtheria based upon clinical signs of upper airway obstruction, including open-mouth breathing with the neck extended. Loud inspiratory stridor was observed in all cases.

Medical therapy protocol

Two medical therapy protocols based upon estimated days to slaughter were used in the treatment of diphtheria at the feedyard where this surgery was developed.

Protocol 1. On day 1 after being identified with diphtheria, calves were administered oxytetracycline[a] (5 mg/lb [11 mg/kg] body weight (BW) intravenously, tylosin[b] (8 mg/lb [17.6 mg/kg] BW intramuscularly (IM)), and dexamethasone[c] (10 mg/calf IV). On day 2 calves again received oxytetracycline and tylosin at the same dose as day 1. In addition, sulfamethazine boluses[d] (1 bolus/200 lb [90.7 kg] BW) were administered orally on day 2. On days 3 and 4, calves were again administered oxytetracycline and tylosin.

Protocol 2. On day 1 after being identified with diphtheria, calves were administered ceftiofur sodium[e] (1 mg/lb [2.2 mg/kg] BW subcutaneously) and dexamethasone.[c] On days 2 and 3 calves were retreated with ceftiofur sodium. Calves were evaluated daily and administered ceftiofur sodium on days 4 and 5 if they were not responding to treatment.

Protocol 1 was used first when the estimated days to slaughter was ≥ 28 days so that the animal could be marketed with its pen mates. If the Protocol 1 treatment failed or if the estimated days to slaughter were < 28 days, then Protocol 2 was administered. If the Protocol 2 treatment failed, then calves were eligible for surgical treatment. Label withdrawal times were followed for all products administered.

Surgical treatment for medically non-responsive cases

Surgical equipment was prepared prior to restraining the calf in a processing chute. The animal was secured in a chute using the squeeze, and sometimes a bar was placed behind the calf to press the shoulders against the front head catch. After the animal was in position, a halter and nose tongs were used to elevate and stabilize the head dorsally as far as the chute would allow to maximize neck exposure (Figure 1A). The hair on the ventral neck was clipped in an area approximately 3 inches (in) (7.62 cm) rostral from the angle of the mandible to 4 in (10.16 cm) from the base of the neck, and 6 in (15.24 cm) on both sides of midline. Surgical scrub and aseptic preparation techniques were performed. A surgical drape was not used for the procedure because the drape was not practical to use in a feedyard setting.

Local anesthesia was administered via a local line block with lidocaine[f] (approximately 40 mL) beginning 2 in (5.08 cm) rostral to the angle of the mandible on the midline extending caudally 6 in (15.24 cm) from the edge of the larynx to approximately the level of the mandible (Figure 1B). No additional analgesic modalities were utilized. A scalpel was used to make a full thickness skin incision from the middle of the larynx to the caudal end of the lidocaine line block (Figure 1C). The subcutaneous fascia was sharply incised with a scalpel, and the fascial layer underneath was bluntly dissected the full length of the incision down to the depth of the sternohyoid muscles. The sternohyoid muscles were bluntly separated to expose the trachea, and the remaining fascia was removed from the trachea. A transverse incision was then made between the fourth and fifth cartilage rings.

As the incision was made into the lumen of the trachea, air and mucous were expelled in many cases. While keeping the other tissues retracted, the larger of the 2 tracheostomy tubes[g] was placed through the tracheal incision and caudally down the tracheal lumen. Then the smaller of the tracheostomy tubes was inserted through the center of the larger tube and placed cranially into the lumen of the trachea. The tracheostomy tubes were locked together with a small latch. When the tubes were locked together, the parts that extend caudally and cranially on the inside of the tracheal lumen secured the tube inside the lumen of the trachea. Once the tube was placed and properly secured, the calf was able to breathe normally.

Closure of the skin was completed with umbilical tape[h] to secure the tube and prevent infection. One simple interrupted suture was placed above and below the neck of the tube underneath the tube's collar to pull the skin together around the tube and secure it externally (Figure 1D). The remaining skin was apposed using cruciate suture placements to allow first-intention healing.

After the surgery was complete, the surgical area was cleaned with an attempt to avoid any water entering into the tracheal tube. The animal was treated for 5 days with

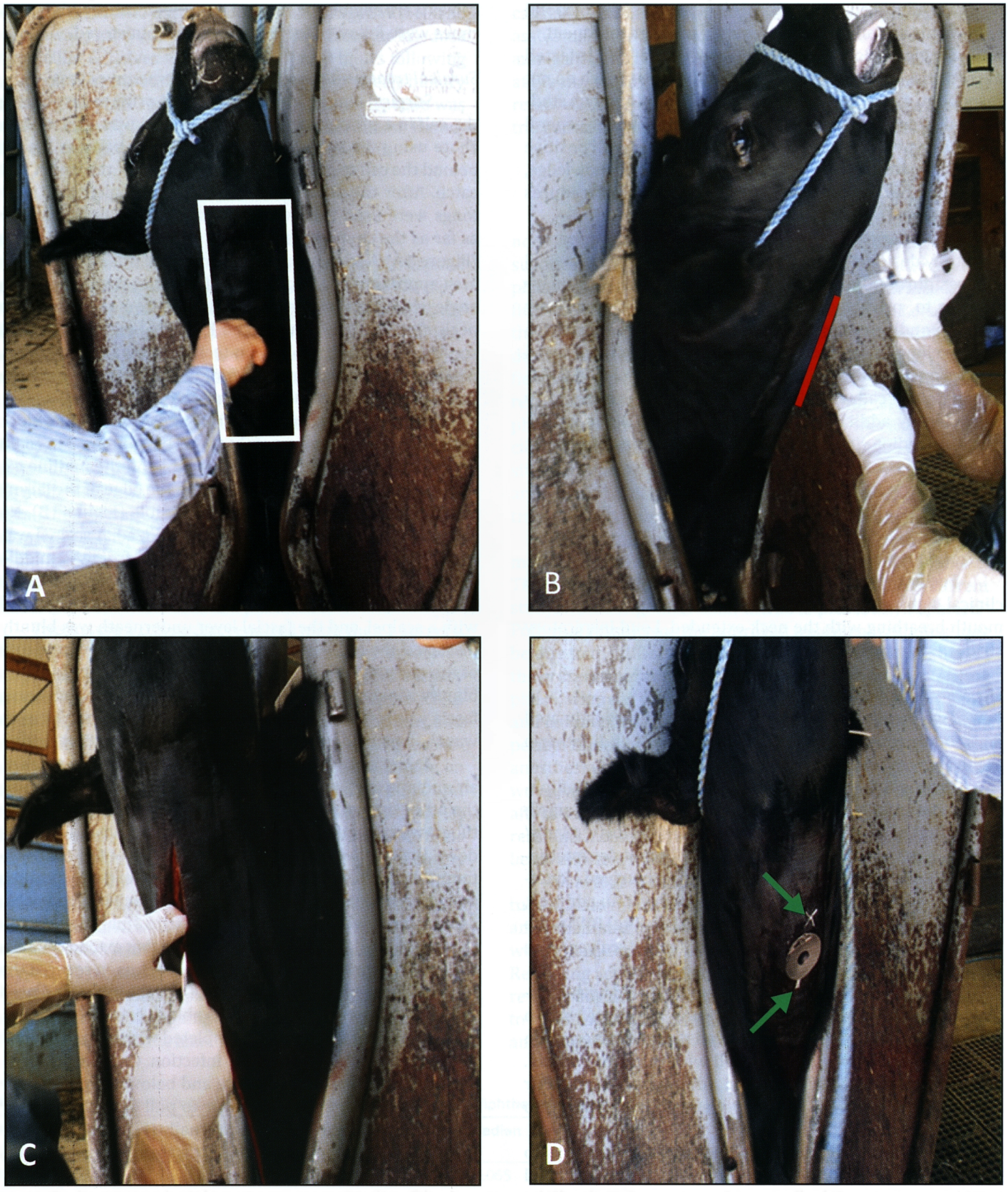

Figure 1. Surgical preparation (A), line block (B), surgical incision (C), and tracheal tube placement and suture (D) for tracheostomy tube placement in medically non-responding diphtheria feedlot cases. White box in A represents clipping area, red line in B represents line block placement, and green arrows in D represent suture placement.

penicillin G[i] (15,000 units/lb [33,069 units/kg] BW IM). The withdrawal period was extended to 14 days from the last dose of penicillin G. Calves were limit-fed for 48 hours following the surgery to reduce risk of bloat if they were overly hungry following surgery. The lumen of the tracheostomy tube was checked daily for 2 days post-surgery for occlusion. Hemostats were used to re-establish patency as needed.

Case Outcomes

Surgical responses

Forty-five calves with diphtheria that failed to respond to antibiotic therapy required surgical intervention. The diphtheria cases in this study occurred during 2010 and 2014; the descriptive statistics for these calves are provided in Table 1. Fourteen of the calves were heifers, and 31 were steers. An increase in appetite and willingness to eat was observed in all of the animals postoperatively.

A total of 42 surgical cases (93%) survived until harvest. The 3 fatal cases were necropsied by feedlot personnel trained under the supervision of the consulting veterinarian. The tracheostomy tube fell out of place in 1 of the cases, and the calf died during surgery to re-insert the tube. The second calf died from chronic bronchopneumonia with lung abscessation. Healing laryngeal lesions were present upon gross necropsy, supporting the history of diphtheria. The third calf died of bloat 2 months after the procedure.

There were 5 calves that required more than 1 surgery. The surgical procedure was repeated exactly the same way except there was some scar tissue from the previous surgery that had to be broken down during the second approach to the trachea. Three calves required 2 surgical procedures, and 2 calves required 3 surgical procedures to replace the tracheostomy tubes. The calves hooked the tracheostomy tube on some object in the pen, usually the edge of the feed bunk, and pulled the tube out of the trachea. Four of the 5 calves (80%) which required multiple surgeries were harvested with their pen cohorts. The fifth calf died during surgery to re-insert the tracheostomy tube (described previously). Two other calves that lost their tracheostomy tubes had no recurrence of respiratory distress, required no additional treatment, and were harvested with pen mates. These calves lost their tubes more than 2 months after surgery.

Another minor complication was obstruction of the tracheostomy tube with organic debris. Hard, crusty organic material accumulated in the lumen of the tube and blocked airflow, causing continued respiratory distress. Based upon subjective assessment, the build-up of organic material often occurred in animals that had excessive drainage from the diphtheria lesion at the time of surgery in the larynx. The organic material was removed using forceps. Most cases required cleaning of the tracheostomy tube once or twice after the procedure.

Discussion

Surgical tracheostomy tube placement in medically non-responding diphtheria cases provides a practical and successful approach to allow calves to complete the feeding phase with their cohorts. The surgery was performed in the field using a chute at the feedlot hospital facility. Local anesthetic using lidocaine was the only analgesic modality used during the study. Being able to perform the surgery in the field and only using lidocaine keeps the cost of the procedure reasonable. Estimated time from last surgical scrub to suture placement was 15 minutes. Umbilical tape was used for skin closure due to its tensile strength and durability. The surgical site was exposed to the concrete feed bunk and water tanks, and the umbilical tape provided very good stability for the tracheostomy tube while the incision was healing.

Calves treated surgically performed similar to their pen mates, as they were all slaughtered with their pen cohorts. The surgery was successful in 93% of the cases in the current study, which is greater than the 58% previously reported.[4] Potential reasons for the improved treatment response may be due to the differences in case selection. Feedlot calves in the present study only needed to survive through the feeding phase, whereas previous studies evaluated survival in bulls and cows which were in the production system for a longer period.[4] Gasthuys et al sedated calves and provided inhalation anesthesia in heavier calves plus local anesthesia, whereas we only used local anesthesia.[4] The additional sedation may affect cardiovascular output and case outcomes.[1] Proper restraint in a squeeze chute and local anesthesia appears to be an effective method to perform this surgery in the field.

Previously reported complications of tracheostomy tube placement included obstruction due to organic material and tube loss from the surgical site.[4,10] These complications were infrequent, and were manageable when detected early. Removing accumulated organic material from the airway or re-inserting the tracheostomy tube is a relatively simple way to keep the airway patent. Subjectively, surgical technique and severity of laryngeal abscesses appeared to have the

Table 1. Descriptive statistics of 45 calves treated surgically for chronic diphtheria.

Parameter	Mean	Median	Standard deviation	Quartile 1	Quartile 3
Body weight, lb	1058	1065	167.0	955	1171
Days-on-feed, days	90	81	44.9	58	118
Estimated days to harvest, days	106	99	52.7	70	140
Previous treatment costs, $/animal	80.41	82.29	24.2	71.31	94.79

greatest effect on the amount of organic material which had to be cleaned and removed. A clean surgical area, sterile surgical instruments, and good ventilation minimized the post-operative material in the tube. The tracheal incision needed to be between one third and one half the circumference of the trachea to allow for cartilaginous ring separation. This separation of the tracheal rings prevented bowing of the tracheal lumen at an angle toward the tube and minimized air resistance. Buildup of organic material at the sight of the tube placement is also reduced by preventing bowing of the tracheal lumen. Calves in the current study were monitored by the same person for several days postoperatively. Calves were restrained in a squeeze chute daily for 5 days post-surgery to administer penicillin G, which allowed access to the surgical site for daily removal of organic material.

The 2 calves that lost tracheostomy tubes 2 months after surgery and had no complications provide some interesting results. The obstructed upper airway above the tracheostomy tube may have cleared spontaneously, thereby allowing normal airflow. The calf that died during replacement of the tracheostomy tube died of asphyxia because of the closed airway. However, only 11% (5/45) required multiple surgeries to replace the tracheostomy tube.

Calves that required surgical intervention had been on feed an average of 90 days with an average treatment cost of $80.41/hd (Table 1). Significant resources were invested in each of the calves, including feed, hay, water, medicine, vaccine, equipment, and labor. Significant resources were also invested in the cow that raised the calf. Calves that die in the feedyard provide no return on investment of time, labor and resources. Sustainability of resources is needed, and surgical treatment of medically non-responding chronic diphtheria cases in feedlot cattle is an effective way to preserve resources and optimize the value of these animals at slaughter.

Human resources are a significant investment throughout the cattle production cycle and death losses can be demoralizing for feedlot personnel who care for the cattle every day. Calves requiring surgical intervention in this study had significant treatment costs prior to surgery. Surgery such as described here can be used to salvage cattle, and allow reasonable growth performance until harvest. This can be uplifting for feedlot personnel as well as returning economic reward to the business.

A potential limitation in this case series is the lack of a comparison group to evaluate outcomes in cattle that would have been managed solely with systemic antibiotics; however, based on the well-known negative consequences of morbidity to feedlot performance, it is logical to speculate cattle not responding to medical treatment for diphtheria would not perform as well as cattle treated with both antibiotics and surgery.

Conclusions

Surgical treatment of non-responsive diphtheria cases in feedlot cattle provides a practical option to manage these cases to a successful outcome. Surgery can be performed successfully in a feedyard setting with minimal complications. This case series highlights the value of a practicing veterinarian identifying a problem and developing a practical solution to address it. Results of this study should stimulate more research in management of beef cattle diseases. While the incidence of non-responding diphtheria cases is small, surgical treatment of calves failing to respond to medical therapy provides an option to impact mortality of the affected population and preserve resources as well.

Endnotes

[a] Agrimycin 100 Agrilabs, St Joseph, MO
[b] Tylan 200, Elanco Animal Health, Greenfield, IN
[c] Dexamethasone, Agrilabs, St Joseph, MO
[d] Supra Sulfa III Antibacterial Calf Bolus, Aspen Veterinary Resources, Ltd., Liberty, MO
[e] Naxcel, Zoetis Animal Health, Kalamazoo, MI
[f] Lidocaine HCL 2%, Vedco, St. Joeseph, MO
[g] Tracheotomy Tube Model J-144b, Jorgensen Labs, Loveland, CO
[h] Umbilical Tape Look 1/8 inch, White Braided Polyester, Surgical Specialties Corporation, Wyomissing, PA
[i] Pen-G, Bimeda Inc., Oakbrook Terrace, IL

Acknowledgement

The authors declare no conflict of interest.

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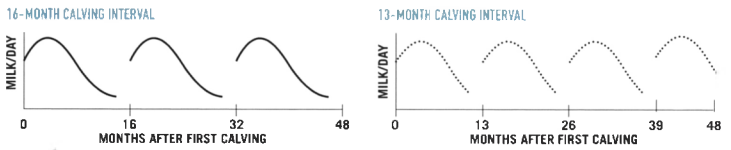

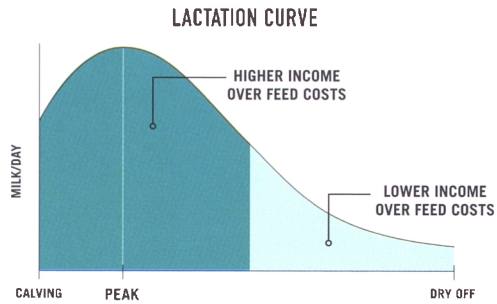

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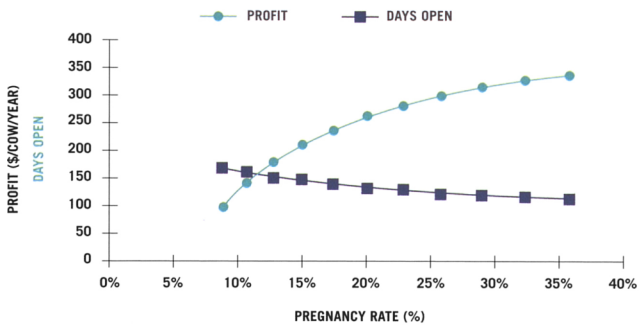

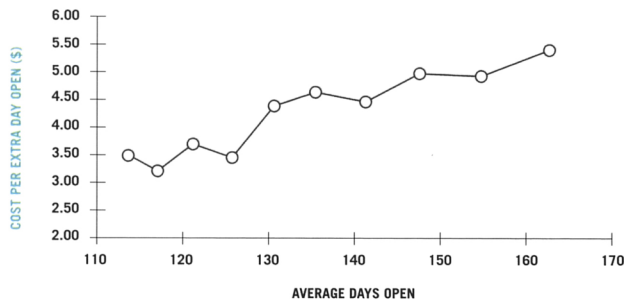

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The Safety Data Sheet (SDS) contains more detailed occupational safety information. To obtain a SDS or for technical assistance, contact Merial at 1-888-637-4251. To report suspected adverse drug experiences, contact Merial at 1-888-637-4251. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/AnimalVeterinary.

PHARMACOLOGY AND TOXICOLOGY:
Endogenous gonadorelin is synthesized and/or released from the hypothalamus during various stages of the bovine estrus cycle following appropriate neurogenic stimuli. It passes via the hypophyseal portal vessels, to the anterior pituitary to effect the release of gonadotropins (e.g., LH, FSH). Synthetic gonadorelin administered intravenously or intramuscularly also causes the release of endogenous LH or FSH from the anterior pituitary.

Gonadorelin diacetate tetrahydrate has been shown to be safe. The LD50 for mice and rats is greater than 60 mg/kg, and for dogs, greater than 600 mcg/kg, respectively. No adverse effects were noted among rats or dogs administered 120 mcg/kg/day or 72 mcg/kg/day intravenously for 15 days.

It had no adverse effects on heart rate, blood pressure, or EKG to unanesthetized dogs at 60 mcg/kg. In anesthetized dogs it did not produce depression of myocardial or system hemodynamics or adversely affect coronary oxygen supply or myocardial oxygen requirements.

The intravenous administration of 60 mcg/kg/day of gonadorelin diacetate tetrahydrate to pregnant rats and rabbits during organogenesis did not cause embryotoxic or teratogenic effects. Further, CYSTORELIN did not cause irritation at the site of intramuscular administration in dogs with a dose of 72 mcg/kg/day administered for seven (7) days.

TARGET ANIMAL SAFETY:
In addition to the animal safety information presented in the PHARMACOLOGY AND TOXICOLOGY section, the safety of CYSTORELIN was established through the review and evaluation of the extensive published literature available for the use of gonadorelin-containing products.

The intramuscular administration of 1000 mcg gonadorelin diacetate tetrahydrate on five (5) consecutive days to normally cycling dairy cattle had no effect on hematology or clinical chemistries.

In field studies evaluating the effectiveness of CYSTORELIN for the treatment of ovarian follicular cysts, the incidence of health abnormalities was not significantly greater in cows administered CYSTORELIN than cows administered a placebo injection.

The target animal safety of, and injection site reactions to, gonadorelin when used with cloprostenol sodium were evaluated during the conduct of effectiveness field studies. The incidence of health abnormalities was not significantly greater in cows administered gonadorelin than cows administered a placebo injection.

EFFECTIVENESS:
The use of CYSTORELIN for treatment of ovarian follicular cysts in dairy cattle was demonstrated to be effective with a treatment dose of 100 mcg gonadorelin diacetate tetrahydrate.

The effectiveness of gonadorelin for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy cows was demonstrated in a field study at 10 different locations in the U.S. Four of the locations represented conditions that would typically cause heat stress in lactating cows. A total of 1607 healthy, non-pregnant, primiparous or multiparous lactating dairy cows within 40-150 days postpartum were enrolled in the study. A total of 805 cows were administered gonadorelin (1 mL; 100 mcg gonadorelin as the acetate salt) and 802 cows were administered an equivalent volume of water for injection as an intramuscular injection twice in the following regimen:

Day 0: 100mcg gonadorelin (as the acetate salt) or sterile water for injection
Day 7: 500 mcg cloprostenol (as cloprostenol sodium)
Day 9: 100mcg gonadorelin (as the acetate salt) or sterile water for injection

Fixed time AI was performed on Day 10, approximately 11 - 31 hours after the Day 9 injection. Cows were evaluated for pregnancy on Day 45 ± 5 days by trans-rectal ultrasound or rectal palpation. Pregnancy rate to FTAI was significantly higher ($P < 0.0001$) in cows treated with gonadorelin (33.4%) than the pregnancy rate to FTAI in cows treated with water (13.6%). The environmental condition (heat stress or not heat stress) did not affect the conclusion of effectiveness. The effectiveness of gonadorelin for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in beef cows was demonstrated in a field study at 10 different locations in the U.S. A total of 706 healthy, non-pregnant, primiparous or multiparous beef cows within 40-150 days postpartum were enrolled in the study. A total of 364 cows were administered gonadorelin (1 mL; 100 mcg gonadorelin as the acetate salt) and 342 cows were administered an equivalent volume of water for injection as an intramuscular injection twice in the following regimen:

Day 0: 100mcg gonadorelin (as the acetate salt) or sterile water for injection
Day 7: 500 mcg cloprostenol (as cloprostenol sodium)
Day 9: 100mcg gonadorelin (as the acetate salt) or sterile water for injection

Fixed time AI was performed immediately after the Day 9 injection. Cows were evaluated for pregnancy on Day 55 ± 5 days by trans-rectal ultrasound. Pregnancy rate to FTAI was significantly higher ($P = 0.0006$) in cows treated with gonadorelin (21.7%) than the pregnancy rate to FTAI in cows treated with water (7.4%).

The effectiveness of a 2-mL dose of CYSTORELIN delivering 100 mcg gonadorelin diacetate tetrahydrate (86 mcg gonadorelin) for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy cows and beef cows was also demonstrated through references to scientific literature.

HOW SUPPLIED:
CYSTORELIN is available in a concentration of 50 mcg/mL gonadorelin diacetate tetrahydrate (43 mcg/mL gonadorelin) pH adjusted with potassium phosphate (monobasic and dibasic).

CYSTORELIN is supplied in multi-dose vials containing 10 mL and 30 mL of sterile solution.

STORAGE, HANDLING, AND DISPOSAL: Store at or below 77°F (25°C). Brief excursions to 86°F (30°C) are permitted. Use within 6 months of first puncture.

NADA 098-379, Approved by FDA

Marketed by:
Merial, Inc.
Duluth, GA 30096-4640 U.S.A.
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Item No. 82830201

SYNCHSURE™
(cloprostenol sodium)
By Merial

Prostaglandin Analogue for Cattle
Equivalent to 250 mcg cloprostenol/mL

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
SYNCHSURE (cloprostenol sodium) is a synthetic prostaglandin analogue related to prostaglandin $F_{2\alpha}$. SYNCHSURE is indicated for intramuscular use at a two mL dose to induce luteolysis in beef and dairy cattle. The luteolytic action of SYNCHSURE can be used to manipulate the estrous cycle to better fit certain management practices, to terminate pregnancies resulting from mismatings, and to treat certain conditions associated with prolonged luteal function.

USES OF SYNCHSURE:

Unobserved or Nondetected Estrus: If a mature *corpus luteum* is present, SYNCHSURE can be used to induce estrus. Estrus is expected to occur 2 to 5 days following injection. Treated cattle should be inseminated at the usual time following detected estrus or twice at 72 and 96 hours post injection if estrus detection is not possible or desirable.

Pyometra or Chronic Endometritis: Endometritis is inflammation of the uterus and pyometra is characterized by the lack of cyclical estrus behavior and the presence of a persistent *corpus luteum*. SYNCHSURE induces luteolysis which usually results in evacuation of the uterus and a return to normal cycling activity within 14 days after treatment.

Mummified fetus: Induction of luteolysis with SYNCHSURE usually results in the expulsion of the mummified fetus from the uterus. (Manual assistance may be necessary to remove the fetus from the vagina). Normal cyclical activity usually follows.

Luteal Cysts: Luteal cysts may cause abnormal cycling patterns in cows. Treatment with SYNCHSURE can restore normal ovarian activity by causing regression of the luteal cyst.

Pregnancies from mismating: SYNCHSURE can be used to terminate unwanted pregnancies in cattle from 1 week after mating until about 5 months of gestation. The induced abortion is normally uncomplicated and the fetus and placenta are usually expelled 4 to 5 days after the injection. The efficacy of SYNCHSURE in inducing abortion decreases after 5 months of gestation, while the risk of dystocia and additional consequences increases.

Controlled Breeding: SYNCHSURE can be used to schedule estrus and ovulation for individual animals or a group of animals to control breeding times. SYNCHSURE can be used in controlled breeding programs through either single or double injection protocols. Only animals with a mature *corpus luteum* should be treated with the single injection protocol to obtain a maximum response to the single injection. Prior to treatment, cattle should be examined rectally and found to be anatomically normal and nonpregnant. Before a controlled breeding program is planned, the producer and his consulting veterinarian should review the operation's breeding history, herd health and nutritional status and agree that a controlled breeding program is practical in that particular situation.

The use information provided here is not comprehensive. Talk to your veterinarian and consult the full prescribing information available at www.synchsure.com for further details on uses of SYNCHSURE.

SAFETY AND TOXICITY: AT 50 and 100 times the recommended dose, mild side effects may be detected in some cattle including increased uneasiness, slight frothing, and milk let-down. The risk information provided here is not comprehensive. To learn more, talk to your veterinarian about SYNCHSURE or call 1-888-637-4251. The full prescribing information can be found at www.synchsure.com.

CONTRAINDICATIONS: SYNCHSURE should not be given to pregnant animals whose calf is not meant to be aborted.

WARNINGS: For animal use only. Do not use in humans. Keep out of reach of Children. Women of childbearing age, asthmatics and persons with respiratory problems should exercise extreme caution with handling this product. In early stages, women may not be aware of their pregnancies. SYNCHSURE is readily absorbed through the skin and may cause abortion and/or bronchiospasms: direct contact with the skin should be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

PRECAUTIONS:
Careful aseptic techniques should be employed to decrease the possibility of post-injection bacterial infection. Antibiotic therapy should be employed at the first sign of infection. The Safety Data Sheet (SDS) contains more detailed occupational safety information. For technical assistance, to request an SDS, or to report a suspected adverse event, contact Merial Technical Support at 1-888-637-4251. For additional information about adverse event reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/AnimalVeterinary.

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