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Isoflupredone acetate as ancillary therapy for bovine respiratory disease in high-risk stocker calves

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ABSTRACT

Bovine respiratory disease (BRD) is the most prevalent and devastating disease in U.S. feedlot cattle. This study evaluated the use of isoflupredone acetate in the treatment of BRD. Crossbred male beef calves (n = 192; body weight = 221 ± 3.9 kg) were acquired in two blocks from regional auction markets and transported to the University of Arkansas Stocker and Receiving Cattle Unit. Calves were observed daily for signs of respiratory illness. Antibiotic treatment was administered if calves displayed signs of respiratory illness and rectal temperature was ≥40 °C. Calves (n = 72) requiring antibiotic treatment were assigned randomly to either treatment 1 (florfenicol) or treatment 2 (florfenicol plus isoflupredone acetate). Treatment efficacy was determined by rechecking the rectal temperature of treated cattle 48 hours post treatment. Blood was collected (at treatment and recheck) via jugular venipuncture to evaluate complete blood count. Weights were recorded on days 0, 14, 28, 45, and 46. No difference existed for medical cost ($P = 0.54$) or temperature at recheck ($P = 0.43$). Upon recheck, neutrophils were higher and lymphocytes were lower in calves that received isoflupredone acetate ($P \leq 0.04$). No difference existed in overall white blood cell count at recheck ($P = 0.67$). Calves that received isoflupredone acetate tended to exhibit greater ($P = 0.09$) average daily gain (ADG) between days 14 and 28 of the study. Results indicate that using isoflupredone acetate as ancillary therapy in the treatment of BRD did not have a positive effect on overall ADG or medical costs.

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MEET THE STUDENT-AUTHOR

Claire Crews

I am from Jacksonville, Arkansas, and graduated from North Pulaski High School in 2010. After spending four incredible years at the University of Arkansas, I graduated with a Bachelor of Science degree in Animal Science in 2014. This fall I will begin pursing a Doctor of Veterinary Medicine degree at the University of Missouri.

During my undergraduate career, I was a member of the Pre-Veterinary Club, Animal Science REPS (Representing, Educating, and Promoting Scholars), and Gamma Beta Phi Society. I also played clarinet in the Razorback Marching Band and the University of Arkansas Wind Ensemble. In the winter of 2012, I participated in a study abroad course in Belize in which I had the opportunity to provide free veterinary services to animals owned by low-income families. This experience helped me appreciate the ingenuity of cultures different from my own.

My honors research project was inspired by my desire to improve animal health. I would like to thank Jeremy Powell for helping me develop the topic for my project and for providing me with advice and encouragement throughout my research endeavors. I would also like to thank Elizabeth Kegley, Jana Reynolds, and Pete Hornsby for providing much assistance with the technical procedures of this project.

INTRODUCTION

Bovine respiratory disease (BRD) is the most prevalent and devastating disease in U.S. feedlot cattle. Every year, U.S. feedlot operations experience substantial economic loss due to the pervasiveness of the disease. It is estimated that the U.S. cattle industry experiences an annual economic loss of approximately $1 billion (Griffin, 1997). Preventative and treatment costs are over $3 billion annually.

There are many factors that contribute to the onset of bovine respiratory disease. The disease is often initiated when an animal is exposed to one or multiple stress contributors, such as dust, transportation, overcrowding, commingling with infected animals, weaning, castration, or poor nutrition (Powell, 2010). These stressors cause the animal's immune system to be suppressed, allowing viral and bacterial agents to enter and infect the body. The infection process usually begins with one or more viral agents, such as bovine viral diarrhea (BVD), infectious bovine rhinotracheitis (IBR), parainfluenza type-3 (PI3), or bovine respiratory syncytial virus (BRSV), entering the host in response to a weakened immune system due to various stressors. The viral infection hinders the immune system's ability to fight off infectious bacteria, such as *Mannheimia haemolytica*, *Haemophilus somnus*, or *Pasteurella multiocida*. Bacterial agents cause an even greater infection in the already-impaired respiratory tract, and the accumulation of these agents in the lungs can cause pneumonia (Faber et al., 1999).

Bovine respiratory disease is characterized by depression, isolation from the herd, decreased appetite, increased respiratory rate, fever, coughing, and nasal and/or ocular discharge (Powell, 2010). A clinical illness score (Table 1) should be assigned to any animal identified as sick. A rectal temperature of ≥40 °C (normal temperature = 38.6 °C) is also commonly associated with the disease.

Although antibiotics have been shown to be effective in treating BRD, many consumers are concerned that the excessive use of antibiotics may lead to the development of antibiotic-resistant bacteria in food animals (Hellwig et al., 2000). Non-steroidal anti-inflammatory drugs (NSAIDs) have proven to be beneficial in treating BRD when used in combination with antibiotics (Lockwood et al., 2003). These drugs do not impair the immune system and they help reduce pain and fever (Kaashoek et al., 1996; Lees, 2003). Steroidal anti-inflammatory drugs (SAIDs) have also been used as ancillary therapy, but studies have yielded conflicting results (Christie et al., 1977; Sustronck et al., 1997). These drugs have anti-inflammatory properties, but they are also immunosuppressive (Smith, 1996). Isoflupredone acetate is a SAID that has recently shown favorable results when used as combination therapy. However, only one publication has scientifically evaluated the drug's efficacy in the treatment of BRD. In that study, isoflupredone acetate prevented the

reduction in feed intake and average daily gain (ADG) in the first week after cattle were induced with the disease (Hewson et al., 2011). Faster clinical improvement was also seen in the cattle treated with isoflupredone acetate. Because this drug has not been extensively tested in cattle as ancillary therapy, there is a need for further data. This study was designed to provide supplementary data that can be used to evaluate the use of isoflupredone acetate in the treatment of BRD.

The objectives of this study were to determine the efficacy of isoflupredone acetate as ancillary therapy for bovine respiratory disease and to determine the cost-effectiveness of treatment using isoflupredone acetate as an adjunct to antibiotic treatment versus treatment using solely antibiotics.

MATERIALS AND METHODS

All methods used in this experiment followed the standard protocols that are used at the Stocker and Receiving Unit at the University of Arkansas System Division of Agriculture Experiment Station in Savoy. Additionally, the methods used were reviewed and approved by the University of Arkansas Animal Care and Use Committee.

The study utilized 192 commingled crossbred male beef calves (body weight = 221 ± 3.9 kg) acquired in two blocks (block 1 = 27 Sep 2012, block 2 = 11 Oct 2013). Calves were purchased from regional auction markets and transported to the University of Arkansas Stocker and Receiving Unit. Upon arrival (day -1), calves were individually weighed, identified with a uniquely numbered ear tag, and tested for a persistent infection of bovine viral diarrhea virus (PI-BVDV) using the antigen capture ELISA ear notch test (CattleStats LLC, Oklahoma City, Okla.). Calves were kept commingled overnight and were given ad libitum access to bermudagrass hay and water. The following day (day 0), calves were reweighed, castrated by banding (if applicable), and inoculated with a 5-way modified-live virus vaccine (Pyramid 5, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Mo.) and an 8-way clostridial vaccine (Covexin 8®, Merck Animal Health, Summit, N.J.). Calves were also treated for internal parasites (Cydectin, Boehringer Ingelheim Vetmedica, Inc.). They were then stratified by body weight and randomly assigned to 1 of 8 pens (0.42 ha) so that the average weights of the pens were similar. All calves were fed a grain supplement with a rate adjusted to a maximum of 1.9 kg per day per calf, which met or exceeded all nutrient requirements (NRC, 1996). The pre-determined quantity of feed was hand fed each morning (~8:30 a.m.). In addition, calves were given ad libitum access to bermudagrass hay and water.

Over the course of the 46-day study, all calves were observed daily (~8:00 a.m.) for signs of BRD. If 2 or more signs existed (i.e. depression, decreased appetite, coughing, nasal or ocular discharge), calves were pulled from the group and rectal temperature was recorded via digital thermometer (GLA Agricultural Products, San Luis Obispo, Calif.). If rectal temperature was ≥40 °C, calves were treated with 1 of 2 treatment methods (based on a pre-assigned treatment randomization sheet). Calves assigned to treatment 1 (control) received an injection of florfenicol (6 mL/45.4 kg) (Nuflor, Intervet Schering-Plough Animal Health, Summit, N.J.). Calves assigned to treatment 2 (ancillary therapy) received an injection of florfenicol (6 mL/45.4 kg) (Nuflor, Intervet Schering-Plough Animal Health) plus an injection of isoflupredone acetate (5 mL/45.4 kg) (Predef 2X, Pfizer Animal Health, Kalamazoo, Mich.). All treated cattle were bled via jugular venipuncture (7 mL) into evacuated tubes (Vacutainer, BD Inc, Franklin Lakes, N.J.) upon initial treatment and 48 hours post-treatment to evaluate overall white blood cell (WBC) count. Calves were reevaluated 48 hours post-treatment to determine if further antibiotic therapy was necessary. Usually cattle respond favorably

Table 1. Clinical illness scores (CIS) for calves.

Score	Description	Appearance
1	Slightly ill	Mild depression, gaunt, +/- ocular/nasal discharge
2	Moderately ill	Ocular/nasal discharge, lags behind other animals in the group, coughing, labored breathing, moderate depression, +/- rough hair coat, weight loss
3	Severely ill	Severe depression, labored breathing, purulent ocular/nasal discharge, not responsive to human approach
4	Moribund	Near death

Powell, 2010.

(80-85%) to the first line of treatment and no additional treatment is necessary (Edwards, 2010). Subsequent antibiotic therapy was administered if rectal temperature was still ≥40 °C or if the clinical illness score was greater than the initial score. Therapy 2, consisting of enrofloxacin (5.7 mL/45.4 kg) (Baytril, Bayer Animal Health, Shawnee Mission, Kan.), was given if calves failed to respond to the initial antibiotic therapy. Enrofloxacin was also administered if calves responded to therapy 1 but relapsed less than 21 days after receiving therapy 1. Therapy 3, consisting of ceftiofur hydrochloride (2 mL/45.4 kg) (Excenel, Pfizer Animal Health), was administered if calves did not respond to therapy 2 after 48 hours. Calves that did not respond to therapy 3 were considered "chronic" and were given no further antibiotic treatment. Therapy 3 was also used for calves that responded to therapy 2 but relapsed less than 21 days after receiving it.

Throughout the study, data were recorded for treatment groups 1 and 2 on the basis of morbidity (fever reduction, repull rate, rate of clinical improvement, failed treatments, chronic illness), performance (ADG and total weight gained) and economics (cost of treatments). Blood samples were analyzed using a Cell-Dyn 1700 Hematology Analyzer (Abbott Laboratory, Abbott Park, Ill.). Data were analyzed using the MIXED procedure of SAS (SAS Institute Inc, Cary, N.C.) to compare the effectiveness of the two treatment methods.

RESULTS AND DISCUSSION

Seventy-two out of 192 calves received treatment for respiratory illness. Thirty-eight calves received the control and 34 calves received the ancillary therapy (Table 2). Antibiotic treatments occurred between day 2 and day 14 of the study. Body weights were recorded on day 0, 14, 28, 45, and 46. Average daily gain over the entire 46-day study was not different ($P = 0.88$) between treatment groups (Table 3). Calves that received isoflupredone acetate tended to exhibit greater ($P = 0.09$) ADG between day 14 and day 28 of the study compared to calves that received only antibiotic therapy, 1.06 kg and 0.77 kg, respectively (Table 3). This result contrasts a study conducted by Hewson et al. (2011), in which there were no differences in ADG throughout the study between calves that received isoflupredone acetate and calves that received only antibiotic therapy. No difference was evident between treatment groups for medical cost ($P = 0.54$) or repull rate ($P = 0.53$) (Table 2). Body temperature at recheck ($P = 0.43$) was also not different between treatment groups (Table 2). In Hewson's study (2011), body temperature was normalized sooner in the group that received isoflupredone acetate than in the group that received antibiotic therapy alone.

Upon recheck, neutrophils were higher and lymphocytes were lower in calves that received isoflupredone

Table 2. Effects of isoflupredone acetate as ancillary therapy for bovine respiratory disease on morbidity.

	Antibiotic treatment	Antibiotic treatment with isoflupredone acetate	*P*-value
Number of calves	38	34	--
Time to second pull, days	9	13	0.37
Calves treated two times	9	6	0.53
Repull rate, %	24	18	0.53
Calves treated three times	4	3	0.81
Second relapse, %	44	50	0.83
Medical cost, $	21.73	23.40	0.54
Temperature at treatment, °C	40.4	40.6	0.31
Temperature at recheck, °C	39.5	39.4	0.43

Table 3. Effects of isoflupredone acetate as ancillary therapy for bovine respiratory disease on growth performance.

Average daily gain (ADG) period	Antibiotic treatment	Antibiotic treatment with isoflupredone acetate	*P*-value
Day 0 to day 14, kg	1.23	1.03	0.27
Day 14 to day 28, kg	0.77	1.06	0.09
Day 28 to day 46, kg	0.87	0.76	0.49
Total, kg	0.95	0.94	0.88

acetate ($P \leq 0.04$) compared to calves that received only antibiotic therapy (Table 4). Consequently, the neutrophil to lymphocyte ratio was greater ($P < 0.01$) in calves that received isoflupredone acetate (Table 4). A higher neutrophil to lymphocyte ratio is an indication of stress which, in the case of this study, resulted from the administration of a drug that acts much like the natural stress hormone cortisol. It has been suggested that stress and viral infections may inhibit the recruitment of neutrophils to the lungs leaving a higher number in the peripheral blood (Caswell, 2014). No difference existed in overall WBC count at recheck ($P = 0.67$) (Table 4). This contrasts a study conducted by Sustronck et al. (1997) in which overall WBC count was significantly lower at recheck in calves that received a SAID (flumethasone) in addition to antibiotic therapy in comparison to calves that received only antibiotic therapy.

Results indicate that treatment of bovine respiratory disease with isoflupredone acetate as ancillary therapy to an antibiotic regimen did not have a positive effect on overall ADG or medical costs. The reason that a SAID rather than a NSAID was chosen as ancillary therapy in this study, despite conflicting results, is because SAIDs block molecules higher in the inflammatory cascade (Tsurufuji et al., 1981). It was thought that cattle treated with a SAID in addition to antibiotics would recover faster from BRD because they would not experience the negative effects that occur as a result of the inflammatory response. Isoflupredone acetate, in particular, was chosen in this study because it showed favorable results in the treatment of BRD during a study conducted by Hewson et al. (2011). The reason for the contrasting results between the current study and the study conducted by Hewson and colleagues is unknown. Perhaps replicating the current study using a larger sample group would yield results similar to those of Hewson and colleagues. Further research of isoflupredone acetate is needed in order to better evaluate the drug's effects on body weight gain performance and treatment expense. If this drug shows promising results in future studies, it could help prevent economic loss in the cattle industry due to poor performance, reduced carcass value, or death.

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Table 4. Effects of isoflupredone acetate as ancillary therapy for bovine respiratory disease on blood count analysis.

	Antibiotic treatment	Antibiotic treatment with isoflupredone acetate	*P*-value
At treatment			
White blood cells, n x 10^3/μL	10.7	10.8	0.96
Neutrophils, n x 10^3/μL	4.0	4.2	0.74
Lymphocytes, n x 10^3/μL	4.4	4.3	0.85
Neutrophil:Lymphocyte	1.0	1.1	0.73
Monocytes, n x 10^3/μL	0.7	0.7	0.44
Platelets, n x 10^3/μL	381.1	400.5	0.54
48 hours post treatment			
White blood cells, n x 10^3/μL	10.2	10.4	0.67
Neutrophils, n x 10^3/μL	3.4	4.3	0.01
Lymphocytes, n x 10^3/μL	4.9	4.1	0.04
Neutrophil:Lymphocyte	0.8	1.1	< 0.01
Monocytes, n x 10^3/μL	0.8	0.7	0.25
Platelets, n x 10^3/μL	405.0	438.0	0.25

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