5-2014

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

Claire E. Crews
University of Arkansas, Fayetteville

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An Undergraduate Honors Thesis

in the

Department of Animal Science

Submitted in partial fulfillment of the requirements for the
University of Arkansas
Dale Bumpers College of Agricultural, Food and Life Sciences
Honors Program

by

Claire Crews

May 2014

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Abbreviations:

ELISA	enzyme-linked immunosorbent assay
ADG	average daily gain
BRD	bovine respiratory disease
BW	body weight
PI-BVDV	persistent infection of bovine viral diarrhea virus
WBC	white blood cell

Introduction:

Bovine respiratory disease (BRD) is the leading cause of illness and death in U.S. feedlot cattle. A 1999 study reported that the disease occurred in 14.4% of cattle placed in feedlots (USDA-APHIS, 2001). 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. Such economic loss comes from two main sources—costs associated with prevention, treatment, and mortality and costs associated with decreased performance.

Prior to being transported to the feedlot calves are sometimes preconditioned, though this can be costly. The purpose of preconditioning is to prepare calves for various infectious challenges, as well as to minimize the stress level of calves upon entry into the feedlot. Preconditioned calves are usually weaned (45 days prior to being sold), castrated, treated for internal parasites, and given appropriate vaccines (Powell, 2010). In the commercial feedlot industry, cattle come from many different locations, and they are exposed to many different pathogens, which can be spread among the herd upon arrival at the feedlot. Since feedlot cattle are at a high-risk for contracting BRD, feedlot managers often vaccinate all newly received cattle with a 4- or 5-way viral vaccine and administer a booster vaccine 2 to 4 weeks later (Edwards, 2010). Another common method used to prevent BRD in high-risk groups of cattle is to

administer metaphylactic antibiotic therapy—the mass medication of a high-risk group of animals to minimize the chance of a potential disease outbreak (Powell, 2010). It has been estimated that preventative costs account for 2-6% of the total cost of production (Griffin, 1997). This is small compared to the costs associated with treatment and mortality. Faber and colleagues (1999) reported that the average treatment cost per animal was $12.39. Bovine respiratory disease was responsible for 87% of the cost of treatment for all diseases. The net profit for treated cattle was $57.48 per head less than for non-treated cattle. Of this net profit difference, 82% was due to the costs of treatment and mortality. The other 18% was attributed to the improvement in growth performance and carcass traits in cattle not treated for the disease. Non-treated cattle experienced a higher net profit because the costs associated with medication and death loss were lower, and the cattle exhibited greater performance in the feedlot due to the absence of the disease. In considering the costs associated with decreased performance there are many facets of influence, not all of which can be accurately measured. In order to fully understand the implication of these costs it is important to understand the cause of the disease and the symptoms that lead to a decrease in performance.

There are many factors that contribute to the onset of bovine respiratory disease. The disease results from a complex interaction between infectious viral and bacterial pathogens, the environment, and the host (Faber et al., 1999). 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). Since the early feedlot period is generally when BRD affects cattle, early detection and treatment are critical in order to prevent economic loss due to poor performance, reduced carcass value, or death.

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 should be assigned to any animal identified as sick. The four clinical illness scores are outlined in Table 1. A rectal temperature of ≥ 40 °C (normal temperature = 38.6 °C) is also commonly associated with the disease. In addition to the initial clinical signs of the disease, there are other less obvious symptoms**.** Bacterial agents colonize in the lungs and induce inflammation, which can lead to severe lung damage if the infection is not detected and treated in the acute phase of the disease (Ramirez-Romero, Brogden, 2000). There is also evidence suggesting that the host's excessive inflammatory response affects the severity of the lung damage. Lung lesions decrease the animal's feedlot performance through a decrease in ADG (Wittum et al., 1996). It is often difficult to classify BRD because other diseases may cause an animal to display similar clinical signs (Wittum et al., 1996) or the animal may hide signs of illness as an instinctive means of protection (Edwards, 2010). According to a study conducted by Wittum and coworkers (1996), 22% of cattle treated for respiratory disease did not have lung lesions at slaughter. Four possible explanations for this outcome are given: the cattle

may have received antibiotics in the acute stage of the disease which prevented permanent lung damage from occurring; the infection was contained in the upper respiratory tract so lung lesions were unable to form; the infectious agents present did not cause lung lesions; or the cattle did not, in fact, have BRD but displayed similar clinical signs. Of the cattle used in the study, 35% were treated for respiratory disease, but at slaughter, lung lesions were present in 72% of all cattle in the experiment—78% of treated cattle had lung lesions and 68% of untreated cattle had lung lesions. This indicates that a large number of cattle had respiratory tract infections but were left untreated. The challenge of identifying subclinical signs associated with BRD may be responsible for an improper identification of the disease. It has been suggested that a better means of classifying BRD is needed in order to prevent such a misdiagnosis.

Once bovine respiratory disease has been diagnosed, one must decide upon the appropriate treatment method. Each cattle facility should establish a sound treatment protocol that defines a sick animal, time to treat, drug(s) to use for treatment, duration of treatment, and when retreatment is necessary (Sweiger and Nichols, 2010). The treatment protocol generally consists of three lines of treatment (Powell, 2010). Sick cattle are given the first line of treatment and are rechecked 48 to 72 hours later for signs of improvement (i.e. lowered rectal temperature and clinical illness score). If cattle exhibit no signs of improvement, they are given the second line of treatment. After 48 to 72 hours cattle are rechecked, and if there is still no favorable response to treatment cattle are given the third and final line of treatment. If cattle fail to show improvement from the third line of treatment, they are considered to have a chronic illness and are given no further treatment. Usually cattle respond favorably (80-85%) to the first line of treatment and no additional treatment is necessary (Edwards, 2010).

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 (NSAID) have been shown to be a useful method for treating BRD when used as an adjunct to antibiotics (Lockwood et al., 2003). These drugs do not impair the immune system and have antipyretic and analgesic effects (Kaashoek et al., 1996; Lees, 2003). A study evaluating the efficacy of three NSAID—flunixin, ketoprofen, and carprofen—found that when used as combination therapy with ceftiofur these drugs caused a more significant reduction in fever than did ceftiofur alone (Lockwood et al., 2003). The extent of lung lesions was reduced by all four treatments, but the greatest reduction occurred from using flunixin. Overall clinical success rates were not significantly different among the four treatment groups. Another study, however, showed that treatment success was greater when a NSAID (flunixin meglume) was used than with the use of an antibiotic (tilmicosin) alone (Hellwig et al., 2000). Repull rate was lower and total medical costs per animal were less in the group treated with flunixin meglume versus the group treated with tilmicosin only, $14.66 and $18.10 respectively. In addition, meloxicam has been shown to be effective when used as adjunct therapy in improving performance traits in animals with BRD. Friton and colleagues (2005) noted that animals treated with meloxicam had higher mean live weights and carcass weights than animals in the control group. The group treated with meloxicam had considerably fewer cases of fever and a much lower mean rectal temperature. In cattle in which lung lesions were present, the ones treated with meloxicam had a smaller area affected than did the control group. The number of clinical relapses and new cases of BRD were similar in the two groups. Thus, NSAID have been shown to be effective in the treatment of BRD.

Steroidal anti-inflammatory drugs (SAID) have also been used as ancillary therapy, but studies have yielded conflicting results. These drugs have anti-inflammatory properties but are immunosuppressive (Smith, 1996). An earlier study used dexamethasone as ancillary therapy and it resulted in poorer response to treatment, higher relapse rate, and slower recovery from the disease (Christie et al., 1977). In another study comparing NSAID meloxicam to SAID flumethasone when used in combination with oxytetracycline, results indicated that meloxicam was more effective in normalizing body temperature and ridding the animal of disease (Bednarek et al., 2003). However, Sustronck and colleagues (1997) reported that SAID may be an effective method for treating BRD. When flumethasone was used in combination with sodium ceftiofur the mean body temperature throughout treatment was lower and animals returned to normal health faster. Additionally, no deaths occurred in the treatment group receiving flumethasone, but deaths did occur in the control group and the group receiving solely sodium ceftiofur. Isoflupredone acetate is another SAID that has 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 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.

Objectives:

To determine the efficacy of isoflupredone acetate as ancillary therapy for bovine respiratory disease; 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 Division of Agriculture Experiment Station in Savoy. In addition, the methods used were reviewed and approved by the University of Arkansas Animal Care and Use Committee.

Commingled crossbred male beef calves (n = 192; BW = 221 ± 3.9 kg) were acquired in two blocks (block 1 = 27SEP2012, block 2 = 11OCT2013) from regional auction markets and transported to the University of Arkansas Stocker and Receiving Unit located near Savoy. 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, OK). Calves were kept commingled overnight and were given ad libitum access to bermudagrass hay and water. The following day (day 0), calves were reweighed and castrated by banding (if applicable). Calves then received a 5-way modified-live virus vaccine (Pyramid 5, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO), an 8-way clostridial vaccine (Covexin 8®, Merck Animal Health, Summit, NJ), and a dewormer (Cydectin, Boehringer Ingelheim Vetmedica, Inc.). They were then stratified by body weight and allocated randomly to 1 of 8 pens (0.42 ha) such that average pen weights 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). In

addition, calves were given ad libitum access to bermudagrass hay and water. The pre-determined quantity of feed was hand fed each morning (~8:30 a.m.).

During the 46-day receiving period, 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, CA). 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, NJ). 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, MI). All treated cattle were bled via jugular venipuncture (7 mL) into evacuated tubes (Vacutainer, BD Inc, Franklin Lakes, NJ) upon initial treatment and 48 hours post-treatment to evaluate overall WBC count (neutrophils, lymphocytes, monocytes, basophils, eosinophils). Calves were re-evaluated 48 hours post-treatment to determine if further antibiotic therapy was necessary. The initial antibiotic therapy usually has an 80-85% efficacy rate, but in some instances follow-up treatment may be 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, KS), 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.

Over the course of the study, data were recorded for treatment groups 1 and 2 on the basis of morbidity (clinical illness score, 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, IL). Data were analyzed using the MIXED procedure of SAS software (SAS Institute Inc, Carry, NC) 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. Antibiotic treatments occurred between day 2 and day 14 of the study. Body weights were recorded on days 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 and colleagues (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 acetate ($P \leq 0.04$) compared to calves that received only antibiotic therapy (Table 4). Consequently, the neutrophil to lymphocyte ratio was higher ($P < .01$) 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, 2013). No difference existed in overall WBC count at recheck ($P = 0.67$) (Table 4). This contrasts a study conducted by Sustronck and coworkers (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. A larger sample group is needed in order to better evaluate the drug's effects on body weight gain performance and treatment expense.

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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)

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, calves	38	34	--
Time to second pull, days	9	13	0.37
Treated twice, calves	9	6	0.53
Repull rate, %	24	18	0.53
Treated thrice, calves	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.

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

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