Ancillary bovine respiratory disease therapy: What adding something with an antibiotic does for our patients

Michael D. Apley, DVM, PhD, DACVCP
College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506

Abstract

Ancillary therapeutics are often administered along with an antimicrobial for the treatment of the bovine respiratory disease complex. For non-steroidal anti-inflammatory drugs (NSAIDs), the majority of clinical trial evidence supports a clear effect of a more rapid decrease in rectal temperature along with some evidence for more rapid improvement in clinical signs as compared to antimicrobials alone. However, there is no clear, consistent clinical evidence to support that NSAIDs result in increased treatment success, reduced case fatality, or improved post-treatment average daily gain as opposed to an antimicrobial alone. It should also be noted that the lumping of all NSAIDs together as a group can result in incorrectly attributing or not attributing important properties to individual drugs. The publicly available information on steroids and vitamin C is much more limited. The only clinical trials involving ancillary therapy with steroids are either negative or neutral. Two trials concerning the use of vitamin C were reviewed, one showing no effects and one presenting a large difference in mortality during the subsequent feeding period, but without enough details to evaluate either internal or external validity.

Key words: bovine respiratory disease, therapy, ancillary

Introduction

The effects of ancillary therapy for bovine respiratory disease have been previously reviewed, in fact quite often. One of the most complete reviews was published in 2012, and these proceedings build on that publication to add additional, more current references as well as Freedom of Information (FOI) studies. These proceedings address the question of whether there are changes in conclusions from the initial review related to the effects of including ancillary therapy with an antimicrobial for treatment of the bovine respiratory disease complex (BRDC). A previous review established that using a non-steroidal anti-inflammatory drug (NSAID) in conjunction with an antimicrobial results in a more rapid decrease in rectal temperature, and in some cases more rapid improvement in clinical signs, but these differences related to antimicrobial-only therapy are short-lived and, as an overall trend in the literature, there is no improvement in rate of gain, feed conversion, case fatality, or first-treatment success.

Lumping all NSAIDs together and making conclusions related to the entire class could result in a misleading extrapolation of effects between individual compounds. However, when general trends apply to the entire class, it is appropriate to mention these observations.

Results of the Previous Review

The previous review, of which the author of these proceedings was a coauthor, searched the literature through 2010 and was published in 2012.[9] The requirements for inclusion in the final review were that the publication must have been in English or French, must have been a clinical trial with naturally occurring bovine respiratory disease (BRD), subjective evaluators must have been masked (blinded), and the study animals must have been randomized to treatment. The treatment groups must have included a control group not receiving the NSAID. Fifteen publications were initially identified, but only 6 clinical trials met all the above criteria.[4,10-13,21] The previous review lists the papers initially identified which were not included in the final analysis, and the reasons for exclusion. All summarized studies evaluated an NSAID; individual clinical trials involved 1) flunixin meglumine, carprofen, and ketoprofen[13], 2) tolfenamic acid[4], 3) flunixin meglumine and diclofenac[11], 4) meloxicam[10], and 5) flunixin meglumine alone[12,21]. While one of the studies included in the previous review involving flunixin met inclusion criteria, an antimicrobial was not administered to the treatment groups; therefore, this publication is not included in this proceedings paper.[21]

The results of the 5 randomized, masked NSAID clinical trials from the previous review included in this proceedings article are summarized in Table 1. Lockwood et al conducted a short 4-day study with only 1 mortality during the study period (in the carprofen group on day 1).[13] All animals were euthanized after the study with evaluation of lung consolidation; there was significantly less lung consolidation in the flunixin treatment group vs no ancillary therapy, with estimated lung consolidation of 19 ± 22.3% for ceftiofur alone and 5.2 ± 13.7% in the ceftiofur-flunixin group.

Friton et al conducted the longest study and reported the only instance of improved weight gain.[10] However, they did not report mortality during the study. Average daily gain for meloxicam and saline control were 2.7 ± 0.57 lb (1.23 ± 0.26 kg) and 2.5 ± 0.4 lb (1.12 ± 0.22 kg), respectively. Thirty-five

percent of control animals and 32% of meloxicam-treated animals had lung lesions at slaughter, with 2.28 ± 3.6 % and 0.50 ± 0.71 % estimated lung consolidation, respectively.

In contrast, Hellwig et al reported no difference in weight gain in stocker calves in a much shorter study.[12] This is the only trial to report an improvement in first-treatment success, which was determined at 48 hours post-treatment and required a drop in rectal temperature below 103.0° F (39.4° C) as compared to a study entry requirement of ≥ 104° F (40° C). Treatment success was 88% for the flunixin group and 61% for the tilmicosin-only group.

The overall conclusions of the authors of this review are as follows, as a direct quote. "… we can conclude that the administration of NSAIDs as an ancillary treatment to BRD causes a more rapid decrease in rectal temperature of the animals without beneficial effects at the end of the treatment on clinical signs. The data also suggest that NSAIDs may decrease lung lesions at the end of the feeding period, but data are either lacking or inconsistent to conclude a potential positive effect on the productivity of treated animals and, consequently, on the positive cost benefits of such treatments. However, one could argue that the initial benefits of NSAIDs may be significant from an animal welfare perspective. The inconsistency of the results concerning the improvements in clinical signs for animals treated with NSAIDs for BRD may mitigate this argument."

Search Protocol for Additional Articles

PubMed and CAB direct searches were conducted for all available years for the combination of respiratory disease and flunixin, meloxicam, diclofenac, aspirin (or acetylsalicylic or salicylate), carprofen, ketoprofen, tolfenamic acid, dexamethasone, isoflupredone acetate, vitamin C, and phenylbutazone. For the aspirin, dexamethasone, and vitamin C searches, a large return of articles related to respiratory disease led to narrowing the search to bovine respiratory disease.

Additional References involving NSAIDS as Ancillary BRD Therapy

Eight additional references related to therapy of naturally occurring acute BRD with an NSAID are included in Table 1. Nickell et al conducted a study where the case definition was directed towards cattle with "mild" respiratory disease by a combination of clinical score criteria and a rectal temperature requirement of > 102.5° F to ≤ 103.9° F (39.2° C to 39.95° C). Clinical outcomes were monitored through day 60, and average daily gain through closeout. Addition of flunixin transdermal to tildipirosin therapy resulted in no changes in first-treatment success, case fatality, or average daily gain.

Mahendran et al focused on a different type of cattle, conducting a 14-day study in preweaned dairy calves up to 10 weeks of age with a case definition of activation of a 103.5° F (39.7° C) fever tag and exclusion of other disease.[14] They found that adding flunixin meglumine to the florfenicol initial treatment protocol yielded no difference in first-treatment success, case fatality, or average daily gain. Ultrasound lung evaluation found no difference in changes in ultrasound lung scores between treatment groups in calves not requiring additional therapy.

Wilson et al evaluated multiple ancillary therapies in conjunction with gamithromycin in a 56-day receiving study involving 320 high-risk calves.[22] No significant difference was found for flunixin meglumine added to the treatment vs gamithromycin alone for first-treatment success, case fatality or average daily gain. Removals were 6.17% for no ancillary therapy and 0% for NSAID ancillary therapy, which was found to be significantly different in a pairwise comparison. Overall mortality and removals for BRD (chronics) combined were 23.8% for no ancillary therapy and 22.5% for NSAID, exhibiting no significant difference.

The 1998 Freedom of Information (FOI) document for flunixin meglumine outlines 2 studies.[8] The first study involves a 14-day study in male Holstein calves 3 to 4 months old treated for naturally occurring BRD with either 3 days of IM 100 mg/ml oxytetracycline, or oxytetracycline in association with flunixin meglumine given daily until rectal temperature was below 104° F (40° C). There was statistically significant improvement in rate of rectal temperature decline and early clinical presentation, but no improvement in first-treatment success. No mortality was reported. Quoting from the FOI document: "Forty percent of the animals in the flunixin plus oxytetracycline group were treatment failures compared to 47% in the oxytetracycline alone group. Forty-four percent of the treatment failures occurred on day 3 in the oxytetracycline alone group, compared to 24% in the flunixin plus oxytetracycline group. Calves receiving flunixin and oxytetracycline gained slightly more weight than the oxytetracycline group over the study (10.1 lb vs 8.8 lb; 4.6 kg vs 4.0 kg, respectively)." No statistical significance was claimed for the difference in weight gain.

The second study reported in this FOI document involved 363 mixed sex, 6 to 12 month old beef cattle observed for 10 days post-treatment. Treatment groups were the same as in the other FOI study discussed above. There was an improved rate of decline in rectal temperature in the flunixin treatment group as well as numerical improvement in initial clinical presentation, although statistical significance of this latter effect is unclear. There was no significant difference for first-treatment success nor case fatality. Discussion of case fatality in the report is quoted here: "Fifteen animals in the group receiving oxytetracycline alone died during the study versus 8 in the group receiving both oxytetracycline and flunixin. One of the study sites had 1 mortality in the oxytetracycline group, and another site had 1 mortality in the oxytetracycline and flunixin group. The third site had a concurrent BVD outbreak. At this site, there were 7 deaths in the flunixin and oxytetracycline group and 14 in the oxytetracycline group." The discussion of the treatment success outcome in the report is also of interest, as it addresses the effect of treatment on the timing of treatment

failures. "Twenty-two percent of the animals in the flunixin plus oxytetracycline group were treatment failures compared to 26% in the oxytetracycline alone group. Thirty-four percent of treatment failures occurred on day 3 in the oxytetracycline alone group, compared to zero in the flunixin plus oxytetracycline group. On day 4, the corresponding percentages were 13% for the group receiving oxytetracycline alone and 10% for the flunixin plus oxytetracycline group."

Thiry et al investigated the response of naturally occurring respiratory disease in 210 crossbred or Holstein cattle, 4 months to 1 year of age, originating from auction markets in Belgium, France, and Spain.[19] The calves were treated with either florfenicol, florfenicol-flunixin meglumine in a combination product, or a saline control. There was initial improvement in clinical presentation and rate of drop in rectal temperature in the florfenicol-flunixin meglumine group as compared to the flunixin only group. These comparisons were by superiority analysis. In contrast, the treatment success rates were analyzed as a non-inferiority study. This type of analysis is based on an *a priori* delta, or percent difference between the groups that, if not exceeded, would be considered proof of equivalence. On day 4, the florfenicol-flunixin group had 99 successes and the florfenicol group had 93 successes, 93.4% and 90.3%, respectively. On day 10, the florfenicol-flunixin group had 71 successes while the florfenicol group had 62 successes, 67% and 60.2%, respectively. Both results met the required amount of difference such that the combination of florfenicol-flunixin meglumine was deemed non-inferior to florfenicol alone.

A study regarding the addition of flunixin meglumine to 300 mg/ml oxytetracycline for the treatment of naturally occurring BRD has been reported in an FOI document.[7] The substantial proof of efficacy in this document involved 2 elements. One was a clinical field study to evaluate the anti-pyretic efficacy of the combined product (successfully demonstrated at 6 hours post-treatment). The second element included pharmacokinetic studies of the original 300 mg/ml product and the oxytetracycline component of the combined product to 1) bridge the oxytetracycline effectiveness data for BRD from the original 300 mg/ml product, 2) demonstrate the bioequivalence of the oxytetracycline component of the combination product for intramuscular and subcutaneous injection, and 3) bridge flunixin effectiveness data from the subcutaneous route to the intramuscular route.

The last acute BRD study discussed here was published by van Donkersgoed et al. The study animals were backgrounded steer calves, 8 to 10 months of age, weighing from 750 to 849 lb (341 to 386 kg). The study was conducted from arrival to terminal weight sort. No significant difference was reported between a single injection of florfenicol, with or without flunixin meglumine, related to first-treatment success, case fatality or average daily gain. Treatment failure rates (first UF relapse) were 19% and 17% for florfenicol and florfenicol-flunixin, respectively. The case fatality rate attributed to BRD and histophilosis was 2.3% for both treatment groups.

Not included in Table 1, which relates to treatment of acute BRD cases, is a 63-day arrival study involving 384 calves administered either tildipirosin or tildipirosin concurrently with transdermal flunixin meglumine at processing.[15] The flunixin group had significantly lower feed intake and ADG during the first 14 days but there were no differences for the subsequent period or overall study. There were no differences in morbidity, mortality, or average daily gain over the entire study period. The authors also monitored the cattle through a daily visual analog scale (VAS) assessment of well-being and monitored activity through collection of accelerometer data. There were no significant differences in activity as monitored by the accelerometers. However, the VAS scores suggested a significant decrease in signs of pain for the flunixin treatment group during the first 36 hours after arrival.

Consideration of other Ancillary Therapy Options for BRD

Corticosteroids. The NAHMS Feedlot 2011 Report indicates that 35.6 ± 5.4% of feedlots with capacities of 1,000 to 7,999 and 19.5 ± 6.1% of feedlots with capacities of ≥ 8,000 head indicated a corticosteroid as a treatment usually given to cattle as part of an initial course of treatment for respiratory disease.[20] There is a paucity of clinical data for using steroids in conjunction with antimicrobials for the therapy of BRD. There is only one clinical study publicly available, of which this author is aware, where dexamethasone was used as an adjunct to an antimicrobial for naturally occurring respiratory disease.[2] In this over 40-year-old study, 1 of 2 treatments was administered to animals identified as displaying clinical signs of BRD. Common drugs for the 2 treatment groups included IV oxytetracycline (5 mg/lb; 11 mg/kg) and IM pyrilamine (250 mg total dose, an antihistamine) daily for 3 days. Treatment group 1 also received 20 mg dexamethasone every day, while treatment group 2 received a 10 ml placebo injection. The same treatments for each group were continued through day 3, as needed, for non-responders with switches to other therapies common to both groups for subsequent therapy as needed. Results are presented in Table 2. Response was significantly different at $P \leq 0.05$ and relapse rate was significantly different at $P \leq 0.01$. How these findings relate to a single injection of dexamethasone is open to conjecture.

These findings aren't that surprising since dexamethasone, at 0.04 mg/kg daily (0.9 ml/100 lb of a 2 mg/ml solution) for 3 days, is used as a research model to suppress neutrophil function in cattle.[17,18] This model was utilized in small Holstein calves in conjunction with induced *Haemophilus somnus* pneumonia to demonstrate that this dexamethasone regimen increased lung lesions.[1] An IBR latency model in rabbits demonstrated that a single high-dose injection of dexamethasone (1.27 mg/lb; 2.8 mg/kg) could bring about reactivation of latent BHV-1.[16] Other studies have failed to show significant differences in treatment response using prednisone acetate,

methylprednisolone, or methylprednisolone succinate in natural and induced respiratory disease.[5,6]

Vitamin C. The NAHMS Feedlot 2011 Report indicates that 4.7 ± 2.5% of feedlots with capacities of 1,000 to 7,999 and 14.9 ± 5.2% of feedlots with capacities of ≥ 8,000 head indicated vitamin C as a treatment usually given to cattle as part of an initial course of treatment for respiratory disease.[20] There are 2 studies available which evaluate the addition of vitamin C to a respiratory disease regimen. Wilson et al, whose results are discussed above for NSAID ancillary therapy, also evaluated vitamin C in conjunction with gamithromycin in a 56-day receiving study involving 320 high-risk calves.[22] No significant difference was found for vitamin C added to the treatment vs gamithromycin alone, for first-treatment success, case fatality or average daily gain. Overall mortality and removals combined were 23.8% for no ancillary therapy and 25.0% for vitamin C, exhibiting no significant difference.

A study in Australia incorporated a study where all calves diagnosed as having BRD were treated with tilmicosin and then every other one of these calves also received 5 grams of vitamin C.[3] The mean weight at time of treatment for the surviving animals which received vitamin C was 799 ± 13.6 lb (363 ± 6.2 kg), giving a mean dose of 16.4 mg/lb (14 mg/kg). The only reported result was that fewer cattle died in the vitamin C group than in the tilmicosin-alone group, 11% vs 23% case fatality, respectively. This seems like an incredible effect for an ancillary therapy. No details are given as to cause or timing of death, and it is noted by the authors that some cattle were excluded from the analysis due to errors in implementation of the treatment protocol, resulting in uneven treatment group size. The publicly available data for vitamin C appear to be conflicting.

Conclusion

The ability of several NSAIDs to decrease rectal temperature more rapidly and in some cases to improve clinical presentation more rapidly have been demonstrated. However, consistent supporting evidence for efficacy related to treatment outcome, case fatality, or average daily gain is lacking for the potential pharmaceutical ancillary therapies for BRD discussed here.

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