Oral meloxicam given as an ancillary treatment at respiratory disease diagnosis was not associated with growth, clinical scores, or ultrasound scores in preweaned dairy calves

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Received June 30, 2023
Accepted August 21, 2023
doi.org/10.2460/javma.23.06.0361
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OBJECTIVE
To assess the efficacy of a single dose of oral meloxicam as an ancillary therapy to an antibiotic given at the time of respiratory disease identification on average daily gain (ADG), behavioral attitude, clinical respiratory, and lung ultrasound scores in preweaned dairy calves.

ANIMALS
215 male and female Holstein, Jersey, and crossbred preweaned calves enrolled between 1 and 14 days of age at study enrollment on a single commercial dairy in the western US.

METHODS
The study took place from March 4, 2021, to November 21, 2021. In this double-blind placebo-controlled study, calves were given an antibiotic (1.1 mL of tulathromycin/kg, SC, once) and either a placebo (1 mg of lactose monohydrate/kg, in a gelatin capsule) or oral meloxicam (1 mg/kg) at the time of respiratory disease identification. Behavioral attitude, clinical respiratory, and lung ultrasound scores and ADG were assessed in preweaned dairy calves at different time points including the next health examination, 1 week later, or at weaning.

RESULTS
There was no association between treatment (placebo vs meloxicam) on ADG or respiratory disease status at weaning (P > .05). There was no effect of treatment on behavioral attitude, clinical respiratory, or lung ultrasound scores at the next health examination or 1 week later (P > .05).

CLINICAL RELEVANCE
The present study did not provide evidence that oral meloxicam given once is beneficial for growth, behavioral attitude, or clinical or lung ultrasound scores.

Keywords: average daily gain, bovine respiratory disease, nonsteroidal anti-inflammatory, behavior, thoracic ultrasound

In 2014, producer-reported data collected through the National Animal Health Monitoring Service estimated that respiratory disease affected 12% of preweaned dairy heifers and accounted for 24% of deaths within this group.1 Previous studies have reported an association between respiratory disease and reduced average daily gain (ADG) in preweaned calves.2–4 Furthermore, calves identified with lung consolidation during the preweaned period had reduced milk production during their first lactation compared to unaffected calves.5 As such, respiratory disease has both short- and long-term consequences that need to be ameliorated.

Respiratory disease develops through a complex interaction between the host’s immune response, stressors, and pathogens.6,7 A calf’s immune system...
responds to pathogens by launching defense mechanisms (eg, secretion of proinflammatory cytokines, recruitment of WBCs, etc) that result in inflammation in the respiratory tract.\textsuperscript{7} Pathogens that invade the lower airway can result in pneumonia, which is inflammation of the bronchi, bronchioles, and alveoli.\textsuperscript{7,8}

Clinical respiratory disease scores (severity scores assigned for nasal and ocular discharge, ear position, cough, and fever) and lung ultrasound scores can be observed over time to assess progression of respiratory disease.\textsuperscript{9-11} Affected calves may also exhibit behavioral changes or sickness behaviors, such as lethargy or decreased grooming and appetite, or exploratory behaviors that may be collectively represented through assigning a behavioral attitude score.\textsuperscript{9,12-14} These changes that accompany respiratory disease can be monitored to determine disease severity and duration, thus providing a means to determine whether a given intervention has ameliorated the effects of respiratory disease.

According to the National Animal Health Monitoring Service,\textsuperscript{1} 94.8% of calves identified with respiratory disease are treated with an antimicrobial. Despite treatment with an antimicrobial, the proportion of preweaned heifer deaths that producers report is due to respiratory disease has remained relatively unchanged over the last 20 years, ranging from 21.3% to 24.0%.\textsuperscript{1,15-18} Additionally, veterinarian respondents in a recent survey\textsuperscript{17} reported administering an average of 2 courses of antimicrobial treatment in a typical case of respiratory disease before clinical signs resolved, suggesting that a single antimicrobial course is not always effective. Moreover, 21% of calves treated with an antibiotic for respiratory disease required retreatment,\textsuperscript{18} and lung lesions identified on ultrasound may decrease in response to antibiotics at first but may recur or worsen after treatment.\textsuperscript{13,18,19}

Given the negative sequelae of respiratory disease coupled with persistently high mortality and repeated treatments, therapies that ameliorate the effects of respiratory disease are needed. NSAIDs represent a potential ancillary therapy for respiratory disease that have not been thoroughly investigated in preweaned calves. The use of NSAIDs is allowable via extralabel drug use with veterinarian approval under AMDUCA.\textsuperscript{20} There is a need for randomized control trials that investigate the effect of NSAID administration to cattle with respiratory disease, as NSAIDs do have the potential to reduce the severity of clinical signs of disease, decrease inflammation-induced lung damage, and reduce growth losses.\textsuperscript{2} For example, a study\textsuperscript{21} of adult fattening cattle with respiratory disease reported greater ADG at 70, 105, and 172 days following treatment with meloxicam and oxytetracycline compared to cattle that received a placebo and oxytetracycline. Friton et al\textsuperscript{22} concluded that cattle that received meloxicam gained 0.11 kg/d more than heifers that received a placebo. Bednarek et al\textsuperscript{22} reported a significantly faster improvement in body temperature in calves that received meloxicam IV as an ancillary therapy compared to calves that received flunixin meglumine as an ancillary therapy and calves that only received an antibiotic. Faster improvement of respiration and depression scores was reported in calves treated with ketoprofen and tulathromycin compared to calves only treated with tulathromycin;

respiratory disease was defined as rectal temperature $\geq 40.0\ ^\circ\text{C}$, respiration score of 2 or 3, and depression score of 2 or 3.\textsuperscript{23} Reduced lung consolidation at postmortem examination 2 to 3 days after treatment in beef cattle\textsuperscript{24} and at slaughter 105 days after treatment\textsuperscript{21} was observed in cattle treated with an NSAID compared to an antibiotic alone. Measuring improvements in ADG as well as attitude, clinical respiratory, and lung ultrasound scores would indicate at least some of the negative effects of respiratory disease.

To our knowledge, oral meloxicam has not yet been evaluated as an ancillary therapy for its effects on ADG, attitude, clinical respiratory, or lung ultrasound scores in preweaned dairy calves but has been reported to alleviate inflammation associated with painful procedures such as castration and disbudding in calves.\textsuperscript{25} Meloxicam is an NSAID with antipyretic and analgesic properties that may aid in alleviating inflammation associated with respiratory disease\textsuperscript{26} and ultimately aid in minimizing the effects of respiratory disease on ADG and behavioral attitude, clinical respiratory, and lung ultrasound scores. The desired target of meloxicam is an isoform of the enzyme cyclooxygenase (COX), known as COX-2, which is upregulated in response to inflammatory stimuli.\textsuperscript{3,4,27} Meloxicam acts by preferentially reducing the production of COX-2, preventing or reducing the production of prostaglandins, key mediators in the inflammatory and pain response.\textsuperscript{27} The investigation of oral meloxicam as ancillary therapy is justified by the need for effective therapies to improve ADG, attitude, clinical, and ultrasound scores in calves with respiratory disease, the reported effectiveness of other forms of meloxicam, its reasonable cost and ease of administration. Therefore, the objective of this study was to assess the efficacy of a single dose of oral meloxicam as an ancillary therapy to an antibiotic given at the time of respiratory disease identification on growth and change in attitude, clinical respiratory, and lung ultrasound scores in preweaned dairy calves in a commercial setting. We hypothesized that the administration of oral meloxicam as an ancillary therapy to an antibiotic would preserve growth as well as improve attitude, clinical, and ultrasound scores in preweaned calves with respiratory disease.

**Methods**

This study received approval from the IACUC at Colorado State University (Protocol No. 1541).

**Study overview**

All calves born alive on the study dairy during the study period (March 4, 2021, to November 21, 2021) underwent twice-weekly health examinations by research staff to monitor health status from 1 to 14 days of age until weaning (WEAN) at 40 to 56 days of age. Health examinations assessed calves for respiratory disease status, fecal consistency, navel and joint inflammation, and behavioral attitude score and also included a weight. Upon identification with respiratory disease, calves were randomly allocated to a treatment group. Once a calf
was allocated to a treatment group, they continued to undergo twice-weekly health examinations until WEAN. Research staff continuously performed twice-weekly health examinations on calves not allocated to a treatment group (ie, calves not yet identified with respiratory disease) to screen them for respiratory disease.

**Animals and facilities**

The study population consisted of both male and female Holstein, Jersey, and crossbred preweaned calves on a single commercial dairy in the western US. Calves were housed in a group of approximately 2 to 7 calves for the first 1 to 7 days after birth before being transported across the dairy to an individual plastic or metal hutch (dependent on availability) until weaning. In the beginning of the study (March to May), hutches were bedded with corn stalks, and toward the end of the study (June to December), hutches were bedded with sawdust. Calves were fed according to the dairy protocol and received 4 L of milk divided between 2 feedings via bottle each day until caretakers deemed the calf was large enough, through visual observation, to receive 6 L of milk in the same manner each day. Once moved to the individual hutches, calves had ad libitum access to calf starter and a water bucket that was checked daily and refilled as needed.

**Blood sampling**

Blood samples to measure serum total protein (STP) were collected in the group newborn pen or individual hutches in the first 7 days of life. Samples were collected using a plastic needle hub, needles (20 G X 1 inch; Exelint International Co), and 10-mL red-top vacuum-sealed tubes (BD Vacutainer; Becton, Dickinson and Co). The blood samples were stored on ice packs in a cooler for transportation from the farm to the lab, then centrifuged at 3,000 X g for 15 minutes at 20 °C. A disposable pipette was used to remove the serum and place 1 to 2 drops in a digital refractometer to measure STP as an indicator of passive transfer (Palm Abbe; MISCO Refractometer). The STP results were defined as quality scores according to Lombard et al.,9 as follows: excellent, ≥ 6.2 g/dL; good, 5.8 to 6.1 g/dL; fair, 5.1 to 5.7 g/dL; and poor, < 5.1 g/dL.

**Health examinations**

Respiratory disease was identified using a combination of clinical scoring9 and lung ultrasound scoring. From enrollment to weaning or death, calves underwent twice-weekly health examinations (mean ± SD, 11.37 ± 3.25) and weight estimations using a heart girth measurement (calf weigh tape; Nasco). Our study focused on the outcomes of the health examinations at 3 time points: the subsequent health examination 2 to 3 days after the first identification of respiratory disease (NEXT), the health examination 7 days after the first identification of respiratory disease (WEEK), and the health examination closest to weaning following the first identification of respiratory disease (WEAN).

Similar to methods described by Binversie et al.,9 95% of the health examinations were performed by the first author (LAF) and the senior author (MCC) performed the remainder. MCC trained LAF in clinical scoring and lung ultrasound prior to the start of the study and regularly observed LAF for consistency. All data were collected through the University of Wisconsin Calf Health Scorer tablet application.9 The clinical respiratory score (CRS) ranged from 0 to 3, with 0 being normal and 3 being severely abnormal, and included an evaluation of ear position, ocular discharge, nasal discharge, cough, and rectal temperature. In addition, attitude, joint, navel, and fecal scores were obtained on the same scale but not included in the CRS. A calf was considered to have a positive CRS (CRS+) if it received a score ≥ 2 in ≥ 2 CRS categories. A portable lung ultrasound with a rectal probe (Ibex Pro; E.I. Medical Imaging) was used to evaluate the left and right lungs beginning caudally and progressing cranially.10 The left lung was scanned beginning at intercostal space (ICS) 6 over the left caudal lung lobe, then ICS 5 to ICS 4 over the caudal aspect of the left cranial lung lobe, then ICS 3 and ICS 2 over the cranial aspect of the left cranial lung lobe.10 The right lung was scanned beginning at ICS 6 over the right caudal lung lobe, then ICS 5 over the right middle lung lobe, then ICS 4 and ICS 3 over the caudal aspect of the right cranial lung lobe, and then ICS 2 and ICS 1 over the cranial aspect of the right cranial lung lobe.10 Lung ultrasound was scored on a 6-point scale from 0 to 5 with 0 being normal, ≥ 2 being abnormal, and 5 being severely abnormal.10 The ultrasound scoring system ranged from 0 to 5, where 0 = normal, only normal lung present; 1 = normal, mostly normal lung with diffuse comet tails; 2 = abnormal, lobular pneumonia, area of consolidation ≥ 1 cm²; 3 = abnormal, lobular pneumonia, area of consolidation is 1 entire lung lobe; 4 = abnormal, lobular pneumonia, area of consolidation is 2 entire lung lobes; and 5 = abnormal, lobular pneumonia, area of consolidation ≥ 3 entire lung lobes.10 The additional measurements in the health examination were defined on the 4-point scale of 0 to 3 but not included in the CRS.9 The attitude score was defined as follows: 0 = bright, alert, and responsive; 1 = dull presentation but calf responds to stimulation; 2 = depressed presentation and calf is hesitant to lie down or slow to stand in response to stimulation; and 3 = depressed presentation and calf is not responsive to stimulation.9 The navel score was assigned through a physical examination of the navel for heat, swelling, or discharge and defined as follows: 0 = normal presentation and no heat, swelling, discomfort, or discharge; 1 = navel is slightly enlarged but is not warm or causing discomfort; 2 = navel is slightly enlarged, and calf exhibits some discomfort or discharge; and 3 = navel is obviously swollen with heat and/or discharge and discomfort.29 The fecal score was determined through visual and physical evaluation of a calf’s feces and defined as follows: 0 = normal consistency; 1 = semiformal on bedding but pasty; 2 = loose consistency but does not sift through bedding; and 3 = watery consistency and sifts completely through bedding.29

**Treatment allocation and observer blinding**

Once all calves under observation had received their health examination, the observer utilized both the CRS and lung ultrasound scores to identify the presence and type of respiratory disease. In the present study, respiratory disease was classified at first identification using 3 categories: upper respiratory tract infection (URTI) = calf was CRS+ with a normal ultra-
sound score (< 2); subclinical pneumonia (SCP) = calf was CRS− with an abnormal ultrasound score (≥ 2); and clinical pneumonia (CP) = calf was CRS+ with an abnormal ultrasound score (≥ 2).5,10

Upon first identification of respiratory disease, all calves received tulathromycin (1.1 mL/kg, SC, once) according to the existing farm protocol and were randomly allocated to a treatment group: oral meloxicam (MEL; 1 mg/kg) or placebo (PLA; lactose monohydrate in a gelatin capsule, 1 mg/kg). Calves were randomly allocated using a predetermined randomized list generated in Excel (Microsoft Corp) using the random number function and creating blocks of 10 by respiratory disease type (URT, SCP, or CP) to ensure equal distribution among treatment groups and respiratory disease type. The authors disclose that the use of meloxicam for respiratory disease in preweaned calves in considered extralabel use but is allowable under AMDUCA.20 Prior to the study, the use of meloxicam was discussed with the farm owners, farm veterinarians, and study team, which included veterinarians. The meat withdrawal for meloxicam was established by consulting with the Food Animal Residue Avoidance Databank, which recommended a 21-day meat-withdrawal interval.

The observer performing health examinations was blinded to treatment group allocation for the entirety of the study and throughout statistical analyses. Members of the research team maintained records of all treatments administered, including the calf’s identification number, date of administration, type of respiratory disease identified, name of drug administered, dosage administered, name of the researcher who calculated the dosage, and name of the reviewer who administered the drug. Drug dosage was calculated on the basis of the estimated weight from the heart girth measurement collected at the health examination at the time of allocation similar to Binversie et al.18 To blind the observer performing health examinations, “A” and “B” were used in place of MEL or PLA to label treatment groups during the trial and for analyses. The observer performing health examinations was also not involved in the calculation or administration of MEL or PLA. Farm personnel agreed to report any treatments they administered to calves enrolled in the trial, and farm records were used to identify calves that died during the trial.

Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc). Prior to the start of the trial, a sample size calculation was performed with ADG as the outcome of interest. The calculation determined 80 calves/treatment group were needed, and sample size was inflated by 25% to 35% to account for any death or loss to follow-up that may have occurred. Therefore, our goal was to enroll 100 to 108 calves/treatment group with ≥ 80 calves remaining in each group in the final analyses.

The experimental unit was the calf. The predictor of interest was treatment group (MEL vs PLA), so the final analyses only included calves that were identified with respiratory disease (URT, SCP, or CP) and received MEL or PLA in addition to tulathromycin. The categorical variables evaluated as potential confounders included the following: sex (male or female), breed (Holstein, Jersey, or Crossbreed), season born (0 = Feb to March; 1 = April to May; 2 = June to July; 3 = August to September; and 4 = October to November), respiratory disease type at first identification (URT, SCP, or CP), quality of passive transfer (excellent = ≥ 6.2 g/dL; good = 5.8 to 6.1 g/dL; fair = 5.1 to 5.7 g/dL; poor = < 5.1 g/dL)28, navel (yes = at least 1 score ≥ 2 during observation; no = never had a navel score ≥ 2), diarrhea (yes = 1 score ≥ 3 during observation; no = never had a fecal score ≥ 3). The continuous variables evaluated as potential confounders included the following: the number of days a calf was observed following the first identification of respiratory disease, the calf’s age in days at time of first respiratory disease identification, and the calf’s weight at the first health examination calculated using the heart girth measurement.30 The potential confounders were evaluated using the Spearman correlation, logistic regression, Wilcoxon rank sum test, Fisher exact test, or χ² analysis depending on each variable type. A variable was considered associated with the outcome of interest at P < .2 and offered to the full model for further analysis. Significance for final models was defined as P < .05.

Outcomes

Average daily gain following first identification of respiratory disease until weaning or death was the primary outcome of interest. The ADG (kg/d) was calculated using a linear regression (PROC REG; SAS Institute Inc) with the calf’s age and converted heart girth measurement.31 The categorical variables evaluated as potential confounders included the following: sex (male or female), breed (Holstein, Jersey, or Crossbreed), season born (0 = Feb to March; 1 = April to May; 2 = June to July; 3 = August to September; and 4 = October to November), respiratory disease type at first identification (URT, SCP, or CP), quality of passive transfer (excellent = ≥ 6.2 g/dL; good = 5.8 to 6.1 g/dL; fair = 5.1 to 5.7 g/dL; poor = < 5.1 g/dL)28, navel (yes = at least 1 score ≥ 2 during observation; no = never had a navel score ≥ 2), diarrhea (yes = 1 score ≥ 3 during observation; no = never had a fecal score ≥ 3). A single outcome was assessed at WEAN: respiratory disease status (0 = no respiratory disease at weaning; 1 = URT, SCP, or CP at weaning).

Models

For each model, the predictor of interest was treatment group and no confounding variables were identified. To test the effect of treatment group on ADG, a mixed linear model (PROC MIXED; SAS Institute Inc) was used and included a statement to produce least-squares means estimates ± SEM for ADG by treatment group. Outliers were assessed using studentized residual plots. The effect of treatment group on the proportion of calves in MEL and PLA with a depressed attitude, CRS+, and abnormal ultrasound score (≥ 2) during observation; no = never had a navel score ≥ 2), diarrhea (yes = 1 score ≥ 3 during observation; no = never had a fecal score ≥ 3). A single outcome was assessed at WEAN: respiratory disease status (0 = no respiratory disease at weaning; 1 = URT, SCP, or CP at weaning).

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Results

A total of 215 calves were allocated to treatment groups (MEL, n = 107; PLA, 106), but 190 calves were eligible for final analysis after excluding 11.6% (25/215) from analysis for the following reasons: loss to follow-up due to management decisions to move calves elsewhere on the dairy before weaning (MEL = 2; PLA = 3), lameness (MEL = 4; PLA = 0), maggots infestation (MEL = 1; PLA = 0), lapse in treatment protocol resulting in the calf not being treated at the first identification of respiratory disease but rather at a subsequent identification due to human error (MEL = 2; PLA = 0), receiving the incorrect treatment from what was assigned (MEL = 1; PLA = 0), and improper identification (MEL = 2; PLA = 1). The sample size at each time point varied due to incomplete data and is presented with the results.

One hundred and eighty-nine calves had complete ADG data but 2 outliers were removed, so 187 calves were included in the ADG analysis. One hundred and eighty-one calves were included at NEXT, 165 at WEEK, and 155 at WEAN (Table 1). The randomization method used was successful, as evidenced by the distribution of respiratory disease type between treatment groups in the calves included in the ADG analysis ($P = .9729$), as well as the calves included in each time point: NEXT ($P = .8481$), WEEK ($P = .7260$), and WEAN ($P = .7771$).

Average daily gain

The average (mean ± SD) age of calves at the time of respiratory disease diagnosis with complete ADG data was 23 ± 13 days. The effect of treatment group was not associated with ADG between first identification of respiratory disease until weaning or death ($P = .7139$). The ADG (mean ± SEM) for calves that received MEL was 0.54 ± 0.11 kg/d compared to 0.57 ± 0.10 kg/d in the PLA group.

Attitude, clinical respiratory score, and ultrasound at NEXT and WEEK

The average (mean ± SD) age of calves at the time of respiratory disease diagnosis with complete NEXT data was 23 ± 13 days and for WEEK was 22 ± 13 days. The effect of treatment group was not associated with attitude ($P = .1053$), CRS ($P = .3154$), or abnormal ultrasound score ($P = .2842$) at NEXT, and the effect of treatment group was not associated with attitude ($P = .4552$), CRS ($P = .6910$), or abnormal ultrasound score ($P = .9494$) at WEEK (Table 2).

Table 1—Percentage (n) of preweaned calves in a double-blind placebo-controlled study with each type of respiratory disease, by treatment group and time point.

<table>
<thead>
<tr>
<th>Respiratory disease type</th>
<th>At time of diagnosis</th>
<th>NEXT</th>
<th>WEEK</th>
<th>WEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEL</td>
<td>PLA</td>
<td>MEL</td>
<td>PLA</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>46% (43)</td>
<td>54% (50)</td>
<td>46% (43)</td>
<td>54% (50)</td>
</tr>
<tr>
<td>Subclinical pneumonia</td>
<td>54% (36)</td>
<td>46% (35)</td>
<td>54% (36)</td>
<td>46% (35)</td>
</tr>
<tr>
<td>Clinical pneumonia</td>
<td>47% (8)</td>
<td>53% (9)</td>
<td>47% (8)</td>
<td>53% (9)</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td>94</td>
<td>87</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 2—Frequency of outcomes between treatment groups for calves at NEXT (n = 181) and WEEK (165) that were identified with respiratory disease.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NEXT</th>
<th>Placebo</th>
<th>$P$ value</th>
<th>WEEK</th>
<th>Meloxicam</th>
<th>Placebo</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed attitude</td>
<td>20.7% (18/87)</td>
<td>11.7% (11/94)</td>
<td>.1053</td>
<td>6.3% (5/80)</td>
<td>9.4% (8/85)</td>
<td>.4552</td>
<td></td>
</tr>
<tr>
<td>Abnormal clinical respiratory score</td>
<td>12.6% (11/87)</td>
<td>18.1% (17/94)</td>
<td>.3154</td>
<td>8.75% (7/80)</td>
<td>10.6% (9/85)</td>
<td>.6910</td>
<td></td>
</tr>
<tr>
<td>Abnormal lung ultrasound score</td>
<td>16.1% (14/87)</td>
<td>10.6% (10/94)</td>
<td>.2842</td>
<td>27.5% (22/80)</td>
<td>27.1% (23/85)</td>
<td>.9494</td>
<td></td>
</tr>
</tbody>
</table>

Outcomes included depressed attitude (calf was hesitant to lie down or slow to respond to stimulation or unresponsive to stimulation), abnormal clinical respiratory score (calf had at least 2 abnormal scores for nose, eyes, ears, cough, or fever), and abnormal lung ultrasound score (area of consolidation ≥ 1 cm$^2$).

See Table 1 for key.
Respiratory disease status at WEAN

One hundred and fifty-five calves were included in the analysis at WEAN (Table 1). Forty-three percent (31/73) of calves in the MEL group and 44% (36/82) of calves in the PLA group had respiratory disease at WEAN. The effect of treatment group on respiratory disease status at WEAN was not significant (P = .8572).

Death

Twelve of the 215 calves allocated to a treatment group died during the study (MEL, n = 5; PLA, 7). Of the 12 calves that died, 10 were identified with respiratory disease and 3 had a fever and bloody feces at the health examination prior to death.

Discussion

This study included the use of meloxicam as an ancillary therapy to an antibiotic for respiratory disease in calves, which is considered extralabel drug use of meloxicam. Extralabel drug use was performed with owner consent and complied with provisions of AMDUCA and 21 CFR §530. To our knowledge, this clinical trial was the first of its kind to assess the effects of a single dose of oral meloxicam as an ancillary therapy to an antibiotic for respiratory disease in preweaned dairy calves. Similar to existing literature, our results did not support an association between treatment group and growth, measured as ADG, or health, using attitude, CRS, and ultrasound scores. The outcomes of the present study may be reflective of management factors specific to the enrolled commercial farm, as well as the dosage and frequency chosen for the study.

Average daily gain was not associated with treatment group in our trial, which is consistent with previous findings that NSAIDs are not associated with growth in calves with respiratory disease. All calves in our study received 4 to 6 L of milk/d per the farm’s protocol. Rosadiuk et al defined 4 to 6 L as a low plane of nutrition, and it is possible that the amount of milk provided affected study outcomes. Calves on lower planes of nutrition have less energy to expend, and the calves enrolled in our study may have shifted more energy toward launching an immune response during respiratory disease and had minimal energy left over to contribute to growth, or ADG. For example, calves with respiratory disease in Cramer and Ollivet received 5 L of milk twice per day and gained 0.21 to 0.30 kg/d more than calves in our study. In a study by Mahendran, calves identified with respiratory disease (presence of fever and exclusion of other disease), treated with flunixin meglumine as an ancillary method to an antibiotic, and on a higher plane of nutrition gained 0.11 to 0.12 kg/d more than calves in the present clinical trial. The association between plane of nutrition and the efficacy of NSAIDs as an ancillary therapy for respiratory disease has not yet been reported. However, NSAIDs have been shown to be more effective in calves on a higher plane of nutrition, defined as up to 15 L of milk/d, following disbudding compared to calves on a lower plane of nutrition. The reason we did not observe an effect of treatment group in the present study is potentially explained by the reduced efficacy of NSAIDs on a lower plane of nutrition and calves’ reduced ability to recover from disease on a low plane of nutrition. Plane of nutrition in calves varies on the basis of a calf’s body weight, energy requirements, and environmental conditions (ie, temperature) and should be further investigated as factors affecting the efficacy of NSAIDs on calf growth and health outcomes associated with respiratory disease. In addition, although weight tapes have been validated in calves, a digital scale might detect smaller differences in growth between calves. However, it was not feasible to use a digital scale in the present study given the constraints of the study dairy (ie, remote location, outdoor hutches, uneven ground, mud, snow, etc).

A depressed attitude was not associated with treatment group at NEXT or WEEK in our trial. The half-life of meloxicam is 27 hours; therefore, its effects on calf behavior may not have been observed at NEXT or WEEK that occurred between 48 and 72 hours or 7 days later. As observed in our study, no association between calf demeanor and the administration of an NSAID were observed by Mahendran. Another study of cattle evaluated a combination of ketoprofen and tulathromycin as a treatment for respiratory disease and did not observe an association between treatment and attitude 3 to 14 days following drug administration. The ability to observe the effects of an NSAID may vary on the basis of the time point observations are made postadministration. For example, Mintline et al observed increased play behavior up to 3 hours post-disbudding in calves that received meloxicam but did not observe any behavior differences at 27 hours between calves that did and did not receive meloxicam. In Reedman et al, calves that received meloxicam had decreased pressure sensitivity up to 120 minutes following caustic disbudding compared to calves that did not receive meloxicam, but there were no observed differences in pressure sensitivity at 3 to 4 or 7 days following disbudding. Both Mintline et al and Reedman et al suggest that the analgesic properties of meloxicam have been effective in the short-term in reducing pain associated with disbudding in dairy calves. Although we did not observe an association between NSAIDs and attitude in our study, more research is needed to evaluate the effects of meloxicam on behavior at time points within meloxicam’s half-life.

Clinical respiratory score was not associated with NSAIDs at NEXT or WEEK. This contrasts with other studies that did report a difference in clinical signs of disease between treatment groups. Guzel et al utilized a clinical index score like the clinical scoring system used in our study and did observe an improvement in clinical signs of respiratory disease in the first 48 hours in calves given diclofenac sodium or flunixin meglumine as an ancillary therapy to an antibiotic. Additionally, Bednarek et al observed a significantly faster improvement in clinical signs of respiratory disease.
respiratory disease that was more pronounced in calves treated with meloxicam than calves that did not receive meloxicam 5 days following treatment. The scoring system used in the present study was designed to detect early signs of respiratory disease, whereas the systems used in Bednarek et al18 and Guzel et al19 had definitions meeting more advanced respiratory disease such as dyspnea and a fever of 39.5 °C that may explain the variance in results between studies. Like our study, Guzel et al19 did not observe an effect of treatment on perceived recovery of disease at 7 days following treatment. Though we did not observe an effect of treatment group on clinical signs of disease, existing literature has suggested that providing an NSAID as an ancillary therapy for respiratory disease may aid in the reduced severity of clinical signs of disease in the first few days following treatment. Future research should investigate treatment protocols that may reduce the severity of clinical signs of disease beyond the first few days.

An abnormal ultrasound score was not associated with NSAIDs at NEXT or WEEK. Like the present study, Mahendran15 did not observe an effect of an NSAID as an ancillary therapy on lung ultrasound scores at 48 hours or 14 days following treatment administration. However, Lockwood et al24 reported significantly less abnormal lung tissue in calves treated with flunixin meglumine compared to calves treated with an antibiotic alone through postmortem examinations 1 to 2 days after treatment occurred. Conflicting data suggest the need for future research to determine the effects of providing oral meloxicam, or another NSAID, as an ancillary therapy for respiratory disease on lung ultrasound scores at short- and long-term time points.

A calf’s disease status at weaning is important to evaluate, as calves with lung consolidation are less likely to get pregnant and more likely to be culled before their first parturition.59 Studies with differing methods have reported long-term associations between NSAID administration and incidence of respiratory disease.21,40 Coetze et al40 reported a lower incidence of respiratory disease over a 28-day period in calves that received oral meloxicam (1 mg/kg) upon arrival to the feedlot and at time of castration compared to calves that did not receive oral meloxicam. Friton et al21 observed that 3% fewer cattle previously treated with meloxicam had lung lesions at slaughter than those that did not receive meloxicam upon arrival to the feedlot. Approximately 43% of calves in both treatment groups in the present study had respiratory disease at weaning, which is less than the approximately 80% reported in Binversie et al18 but still represents a large proportion of calves weaned with respiratory disease. Therefore, the present study along with previous studies demonstrating incomplete resolution of disease11,18,19 emphasize the need for further research exploring effective therapies for respiratory disease in calves.

To our knowledge, this study was the first to describe the effects of oral meloxicam as an ancillary therapy for respiratory disease in preweaned calves on growth and health. Although we did not observe an association of NSAIDs and growth or health, our study further demonstrates the need for therapies that effectively ameliorate all aspects of respiratory disease, including growth, clinical signs, lung ultrasound scores, and behavioral attitude. Future studies could consider multiple doses of NSAIDs for their effects on resolution of respiratory disease.

Acknowledgments

The authors thank Grace Larsen for her assistance with data collection and the Graybill Statistics and Data Science Laboratory at Colorado State University for their assistance with data analysis.

Disclosures

Dr. Ollivett is an Associate Editor for the Journal of the American Veterinary Medical Association (JAVMA). She declares that she had no role in the editorial direction of this manuscript. No AI-assisted technologies were used in the generation of this manuscript.

Funding

The authors have nothing to disclose.

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