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Research article

Comparative efficacy of tildipirosin and cefquinome for the treatment of undifferentiated bovine respiratory disease among replacement dairy cattle raised in Chiang Mai Province, Thailand

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Abstract

The objective of this study was to compare the efficacy of tildipirosin and cefquinome for treatment of undifferentiated bovine respiratory disease (BRD) among replacement dairy cattle (calves and heifers) inhabiting dairy farms located in Chiang Mai, Thailand. A total of 52 animals with undifferentiated BRD were enrolled in the study and randomly selected for placement in antibiotic treatment groups. Out of 52 animals, 36 animals were treated with tildipirosin and were subcutaneously given 4 mg/kg body weight once, while 16 animals were treated with cefquinome and were intramuscularly given 1 mg/kg body weight once daily over a period of three days. Physical examinations and clinical attitude scoring (CAS) were performed on Day 1, Day 2, and Day 3 of the treatment periods. The cure rates of the tildipirosin and cefquinome treatment groups were not significantly different ($p > 0.05$) at percentages of 75.0% (27/36) and 87.5% (14/16), respectively. However, for comparisons within groups, rectal temperatures, respiratory rates, and CAS values were observed to have significantly decreased after treatment with both tildipirosin and cefquinome on Day 3 ($p < 0.05$). Furthermore, rumen contraction rate was also significantly increased after treatments with both antibiotics ($p < 0.05$). The degree of efficacy of both antibiotics was similar when the clinical signs and clinical cure rates at the post-treatment point between the two groups were compared. Therefore, the outcomes of this study expand the options for the antibiotic-based treatment of undifferentiated BRD among dairy calves and heifers being raised in this area.

Keywords: Bovine respiratory disease, Cefquinome, Efficacy, Thailand, Tildipirosin

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INTRODUCTION

Bovine respiratory disease (BRD) is a major cause of mortality in young dairy cattle and can result in considerable economic losses (Griffin, 1997; McConnel et al., 2008). The impacts of respiratory disease can be measured by the accumulated economic losses that are associated with mortality and morbidity rates, as well as the treatment and preventive costs that can influence production losses. The BRD has been reported to cost the cattle industry $750 million annually (Griffin, 1997). BRD in cattle is caused by a variety of bacteria and viruses (Cummings et al., 2022). Important bacteria have been implicated in the disease including *Pasteurella multocida* (*P. multocida*), *Mannheimia haemolytica* (*M. haemolytica*), *Mycoplasma bovis* (*M. bovis*), and *Histophilus somni* (*H. somni*) (Cummings et al., 2022). However, these pathogenic bacteria are also found in healthy animals as commensal bacteria in the upper respiratory tract that transform into opportunistic bacteria during incidences of stress or viral co-infection (Booker et al., 2020; Cummings et al., 2022) Previous reports have suggested that *M. bovis* can be a primary cause of the disease or can emerge in cases of co-infection with other pathogens such as *M. haemolytica* (Perez-Casal, 2020). On the other hand, the most common viruses associated with BRD are bovine viral diarrhea virus (BVDV), bovine coronavirus (BCoV), bovine respiratory syncytial virus (BRSV), bovine herpesvirus-1 (BHV-1), bovine parainfluenza virus 3 (BPIV-3), influenza C virus (ICV), and influenza D virus (IDV) (Cummings et al., 2022).

Several studies have reported the prevalence of the BRD at various levels ranging from 4% to 80% (Dubrovsky et al., 2019; Padalino et al., 2021). A study in China reported that *P. multocida*, *H. somni* and *M. haemolytica* were identified as the causes of the BRD with the positivity rate of 8.4%, 4.5% and 2.4%, respectively (Zhou et al., 2023). On the other hand, viruses were also detected in the study including BHV-1 (13.2%), BRSV (5.5%), BVDV (4.9%), BPIV-3 (4.3%), and BCoV (2.2%) (Zhou et al., 2023). However, a few studies in Thailand found that the seroprevalence of *P. multocida* in dairy cows was 71.7%, whereas BVDV, BRSV, BCoV, BPIV-3, ICV, and IDV were detected in BRD calves with the percentage of 71.7%, 52.6%, 40.8%, 10.5%, 68.4%, and 65.8%, respectively (Singhla et al., 2020; Saipinta et al., 2022).

The successful treatment for BRD in cattle is based on early diagnosis and the appropriate drug selection. Increased use of antibiotics in modern animal production has been associated with the emergence of antimicrobial resistant bacteria that have been identified as BRD causative bacteria (DeDonder et al., 2016; Timsit et al., 2017). The resistance to antibiotics of these bacteria can vary by geography. For instance, a study in Iran involving the pneumonic and healthy lungs of slaughtered cattle has suggested that *P. multocida* was resistant to ampicillin, lincomycin, penicillin, rifampin, streptomycin, amoxicillin, erythromycin, and florfenicol (Khamesipour et al., 2018). On the other hand, a study across Europe found that the relevant pathogen was only resistant to florfenicol and spectinomycin (de Jong et al., 2014). Mycoplasmas are intrinsically resistant to β-lactam antimicrobials and sulfonamides because they do not possess a cell wall and do not synthesize folic acid. Mycoplasmas are generally susceptible to antibiotics that affect proteins, such as macrolides, or to nucleic acid synthesis such as that which involves fluoroquinolones (Maunsell et al., 2011). However, BRD in Thailand has traditionally been treated with β-lactam antibiotics such as cephalosporins or penicillin. This has

led to a failure in treatment when BRD has been caused by Mycoplasmas. Tildipirosin is a type of macrolide that is extensively distributed throughout the respiratory tract and is characterized by slow elimination (Menge et al., 2012). This antimicrobial drug is suggested for the treatment of BRD that has been associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* (Bartram et al., 2016; Confer et al., 2016; Zeng et al., 2018). On the other hand, cefquinome, a fourth-generation cephalosporin, is a broad-spectrum antibiotic which is effective against Gram-positive and Gram-negative bacterial species (CVMP, 2003). This antibiotic has been approved for treatment of respiratory tract diseases in cattle and has been used in Thailand for a decade (CVMP, 2003). However, the effectiveness of both antibiotic treatments for BRD has never been studied in replacement dairy cows in the country. Therefore, the purpose of this study was to assess the effectiveness of tildipirosin and cefquinome as methods of antimicrobial treatment for undifferentiated BRD in dairy calves and heifers being raised in Chiang Mai, Thailand.

MATERIALS AND METHODS

Ethical approval

This study was approved by the Animal Care and Use Committee of the Faculty of Veterinary Medicine, Chiang Mai University (FVM-ACUC-R18/2563).

Study site

A prospective study was undertaken for a period from January to December, 2021 involving dairy herds being raised in Mae Wang, San Pa Tong and Doi Lo Districts, Chiang Mai Province. There were 72 dairy farms located in the study area where the average temperature, total precipitation, and average relative humidity were 25.1º C (max = 35.0º C, min = 15.1º C), 1108.0 milliliters, and 70.4%, respectively. The management practices of the farms involving feed resources, feeding protocols, and housing were determined to be similar. Furthermore, all dairy farms included in this study were approved of the Department of Livestock Development of Thailand with regard to their use of good agricultural practice standards.

Animal enrollment

Fifty-two replacement dairy cows without BRD vaccine program and exhibiting clinical signs of undifferentiated BRD from 17 dairy herds were enrolled in the study. These cows were also identified as exhibiting clinical attitude scores (CAS) of 1, 2, 3, and 4 by research veterinarians that administered physical examinations as has been previously described (Skogerboe et al., 2005; Ball et al., 2019). The cows were examined for nasal and ocular discharges, coughing, movement, dyspnea, rectal temperature, and chest auscultation. The criteria of the CASs are presented in Table 1.

All of the replacement dairy cows were of the Holstein-Friesian breed with an average age and body weight of 9 months (min-max = 2-20 months) and 193 kg (min-max = 50-406 kg), respectively. Out of the 52 replacement dairy cows, five cows were male and 47 cows were female, and most cows (76%, 40/52) exhibited the clinical signs of undifferentiated BRD during hot season (February to April).

Table 1 Criteria of clinical attitude score (CAS) for diagnosis of undifferentiated BRD in dairy cows.

CAS	Diagnosis	Clinical signs
0	Normal	- bright, alert, and responsive
1	Mild	- brightens, moves readily, and appears normal - may be mildly depressed and a small amount of nasal or ocular discharge may be present
2	Moderate	- does not brighten up and moves slowly - moderately depressed and may exhibit dyspnea, a considerable nasal or ocular discharge, and coughing
3	Severe	- stumbles or moves only with extreme coercion - severely depressed and may be anorexic and exhibit coughing with copious nasal discharge
4	Moribund	- recumbent and not able or willing to rise or take food and/or water

Exclusion criteria

Replacement dairy cows that had previously received treatment involving antibiotics or antipyretic drugs for any reason, such as in the treatment of respiratory disease or any other diseases before they were diagnosed by research veterinarians, were not enrolled in this study. Furthermore, cows associated with treatment protocol deviations or that had received additional treatment by farm staff were also not approved by the research veterinarians for inclusion in this study.

Treatments

The replacement dairy cows with undifferentiated BRD were randomly selected to be treated with either tildipirosin given subcutaneously at 4 mg/kg body weight once (Zuprevo®; Intervet International GMBH, Unterschleissheim, Germany) or cefquinome (Cobactan®; Intervet International GMBH, Unterschleissheim, Germany) given intramuscularly at 1 mg/kg body weight once daily for three days (CVMP, 2003; Bartram et al., 2016). Flunixin meglumine (Meifluxin®; Thai Meiji Pharmaceutical, Bangkok, Thailand) was administered via intravenous injection by a dosage of 2.2 mg/kg body weight to all cows for anti-pyrexia and anti-inflammation. The animal's weights were measured by a weight tape for calculation of the total volume administration of each drug. The total number of animals in the tildipirosin treatment group and the cefquinome treatment group were 36 and 16 cows, respectively.

Statistical analysis

Clinical cure rates were derived from CAS, rectal temperature, and BRD mortality (Skogerboe et al., 2005). The clinical cure rates were calculated by employing the following equation:

$$\frac{No.\ of\ animals\ completing\ study\ not\ classified\ as\ nonresponder}{No.\ of\ animals\ enrolled} \times 100$$

Non-transformed continuous data associated with rectal temperature or respiratory rate were compared using the Wilcoxon signed-rank test for treatment comparisons within groups on Day 1 and Day 3 (Fowler et al., 2017). Quantitative data involving CASs and locomotion scores were compared by applying Mann–Whitney U test for treatment comparisons between groups at individual time points (Hoar et al., 1998).

RESULTS

Descriptive data

At Day 1 of the tildipirosin group, the cows showed clinical signs of dyspnea, cough, nasal discharge, ocular discharge, and inappetence at the percentage of 50% (18/36), 30.5% (11/36), 44.4% (16/36), 16.7% (6/36), and 69.4% (25/36), respectively. On the other hand, at Day 1 of the cefquinome group, the cows showed clinical signs of dyspnea, cough, and ocular discharge at the same level with percentage of 6.3%, whereas the clinical signs of nasal discharge and inappetence were at the percentage of 31.3% (5/16) and 62.5% (10/16), respectively.

Efficacy of antibiotic drugs

The mortality rates of the tildipirosin and cefquinome treatment groups were 22.2% (8/36) and 6.3% (1/16), respectively. The cure rates for the tildipirosin and cefquinome treatment groups were not significantly different ($p > 0.05$) at percentages of 75.0% (27/36) and 87.5% (14/16), respectively. In the tildipirosin group, out of 36 cows, five and three cows died on Day 2 and Day 3, respectively. On the other hand, only one cow in the cefquinome group died on Day 3. Rectal temperature values, respiratory rates, rumen contraction rate (RCR) and CAS between the tildipirosin and cefquinome groups were also not significantly different on Day 2 and Day 3 of the treatment periods (Table 2). However, the rectal temperatures, respiratory rates, and CAS of the undifferentiated BRD cows within both tildipirosin and cefquinome treatment groups significantly decreased on Day 3 when compared to Day 1 ($p < 0.05$). Furthermore, the RCR within both treatment group significantly increased on Day 3 when compared to Day 1, as is shown in Table 3.

Table 2 Comparison of efficacy between tildipirosin and cefquinome groups for treatment of undifferentiated bovine respiratory disease on Day 2 and Day 3

Parameter	Tildipirosin	Cefquinome	p-value
Avg rectal temperature Day 2 (ºF) [a]	103.3	102.8	0.22
Avg rectal temperature Day 3 (ºF) [b]	102.3	102.0	0.79
Avg respiratory rate Day 2 [c]	59.3.0	51.1	0.18
Avg respiratory rate Day 3 [d]	52.1	47.9	0.28
Avg RCR Day 2 [e]	2.6	2.6	0.72
Avg RCR Day 3 [f]	2.9	2.9	0.54
Avg clinical attitude score day 2 [g]	1.1	1.1	0.21
Avg clinical attitude score day 3 [h]	0.9	0.9	0.63

[a] Average rectal temperature on Day 2 (ºF); [b] Average rectal temperature on Day 3 (ºF); [c] Average respiratory rate on Day 2 (time/minute); [d] Average respiratory rate on Day 3 (time/minute); [e] Average rumen contraction rate on Day 2 (time/2 minutes); [f] Average rumen contraction rate on Day 3 (time/2 minutes); [g] Average clinical attitude score on Day 2; [h] Average clinical attitude score on Day 3

Table 3 Comparison of clinical signs of undifferentiated bovine respiratory disease cows within the tildipirosin and cefquinome treatment groups on Day 1 and Day 3 after treatment

Study group	Parameter	Day 1	Day 3	p-value
Tildipirosin	Avg rectal temperature (ºF) [a]	104.1	102.3	<0.001
Cefquinome	Avg rectal temperature (ºF) [a]	103.7	102.0	0.01
Tildipirosin	Avg respiratory rate [b]	76.6	52.1	<0.001
Cefquinome	Avg respiratory rate [b]	78.3	47.9	0.005
Tildipirosin	Avg RCR [c]	0.7	2.9	<0.001
Cefquinome	Avg RCR [c]	1.1	2.9	<0.001
Tildipirosin	Avg clinical attitude score [d]	1.9	0.9	0.0002
Cefquinome	Avg clinical attitude score [d]	1.8	0.9	0.09

[a] Average rectal temperature (ºF); [b] Average respiratory rate (time/minute)
[c] Average rumen contraction rate; [d] Average clinical attitude score

DISCUSSION

The present study conducted a comparison of the effectiveness of tildipirosin and cefquinome in treating undifferentiated Bovine Respiratory Disease (BRD) among replacement dairy cattle in Chiang Mai province, Thailand. It was observed that the mortality rate in the tildipirosin treatment group was higher than that in the cefquinome treatment group. This may be related to the difference of animals exhibiting BRD clinical signs at Day 1 of each treatment group such as the average rectal temperature and CAS of tildipirosin group was slightly higher than cefquinome group. Furthermore, pathogens caused the BRD were not identified. Therefore, it could be a coinfection with viruses which cannot be treated with the antibiotic and can affect the mortality rate. Notably, a study conducted on feedlot calves in the US reported a mortality rate of 5.2% in calves treated with tildipirosin in combination with flunixin meglumine, while a study in Belgium reported an 8.3% mortality rate in dairy calves treated with tildipirosin for BRD (Bartram et al., 2016; Martin et al., 2020). However, it's worth noting that the first study

involved the prophylactic administration of tildipirosin to feedlot calves upon their arrival, while the latter study administered tildipirosin to dairy calves via *M. bovis* inoculation (Bartram et al., 2016; Martin et al., 2020).

The cure rates between both groups were not found to be significantly different, which aligns with the comparisons made regarding rectal temperatures, respiratory rates, RCR, and CAS in animals from both treatment groups throughout the course of treatment. This suggests that both tildipirosin and cefquinome treatments could be viable options for antibiotic-based treatment of undifferentiated BRD in cattle. Tildipirosin's long-acting nature makes it suitable for non-productive animals such as calves, heifers, or dry cows, reducing the need for animal restraint. Conversely, cefquinome's short-acting characteristic makes it suitable for productive animals, taking into account antibiotic drug residue levels.

Nonetheless, it's important to note that the rectal temperatures of undifferentiated BRD cows significantly decreased within each treatment group before and after treatment. Research has shown that both tildipirosin and cefquinome exhibit efficacy against bacteria associated with BRD, including *P. multocida*, *M. hemolytica*, *H. somni*, and *M. bovis* (Bartram et al., 2016; Confer et al., 2016; Zeng et al., 2018). Importantly, the susceptibility of these bacteria to tildipirosin and cefquinome could enhance the antibiotics' effectiveness in eliminating pathogens and reducing the rectal temperatures of treated animals. This finding is consistent with a study involving calves, which reported low percentages of fever in the tildipirosin treatment group when compared to a negative control group (Bartram et al., 2016).

Respiratory rates in animals from both the tildipirosin and cefquinome groups also significantly decreased after treatment. It has been reported that animals in the tildipirosin treatment group had significantly lower percentages of lung lesions attributed to *M. bovis* in inoculated calves compared to the control group (Bartram et al., 2016). Additionally, a significant reduction in rectal temperature and low percentages of lung lesions resulted in a substantial decrease in respiratory rates among animals at the conclusion of antibiotic treatment (Bartram et al., 2016).

The results regarding RCR and CAS in both the tildipirosin and cefquinome groups mirrored those of rectal temperature and respiratory rate, suggesting a close relationship between these parameters. A study conducted in India indicated that rumen motility increased when fever in sick animals was corrected (Kumar et al., 2015). Furthermore, CAS was derived from rectal temperature and respiratory rate, which explains the similarity in results for these parameters. This finding is in line with the outcomes of a study on the efficacy of tildipirosin for *M. bovis* treatment among calves, which demonstrated lower percentages of days with depression, fever, and abnormal respiratory rates in the treatment group compared to the control group (Bartram et al., 2016).

CONCLUSIONS

The outcomes of this study will provide valuable information related to the efficacy of tildipirosin and cefquinome in the treatment of undifferentiated BRD in dairy calves and heifers in small-holder dairy farms located in Chiang Mai Province, Thailand. The degree of efficacy of both of these antibiotics was similar when the clinical signs and clinical cure rates at the post-treatment point between the two groups were compared. Therefore, the outcomes of this study expand the options for the antibiotic-based treatment of undifferentiated BRD among dairy calves and heifers being raised in this area. However, further study is required to identify pathogens associated with BRD and test for antibiotic drug sensitivity. This would inevitably improve the overall understanding of the causes of BRD and the efficacy of these antibioticssays in dogs with CEs within the context of routine clinical practice.

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AUTHOR CONTRIBUTIONS

A.R. and T.S. designed the study; N.K. and S.P. conducted the field trial and data collection; A.R., T.S. and V.P. analyzed the data and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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