Paper

Randomised positive control trial of NSAID and antimicrobial treatment for calf fever caused by pneumonia

S. A. Mahendran, R. Booth, M. Burge, N. J. Bell

One hundred and fifty-four preweaning calves were followed between May and October 2015. Calves were fitted with continuous monitoring temperature probes (TempVerified FeverTag), programmed so a flashing light emitting diode (LED) light was triggered following six hours of a sustained ear canal temperature of ≥39.7°C. A total of 83 calves (61.9 per cent) developed undifferentiated fever, with a presumptive diagnosis of pneumonia through exclusion of other calf diseases. Once fever was detected, calves were randomly allocated to treatment groups. Calves in group 1 (NSAID) received 2 mg/kg flunixin meglumine (Allevinix, Merial) for three consecutive days and group 2 (antimicrobial) received 6 mg/kg gamithromycin (Zactran, Merial). If fever persisted for 72 hours after the initial treatment, calves were given further treatment (group 1 received antimicrobial and group 2 received NSAID). Calves in group 1 (NSAID) were five times more likely (P=0.002) to require a second treatment (the antimicrobial) after 72 hours to resolve the fever compared with the need to give group 2 (antimicrobial) calves a second treatment (NSAID). This demonstrates the importance of ongoing monitoring and follow-up of calves with respiratory disease. However, of calves with fever in group 1 (NSAID), 25.7 per cent showed resolution following NSAID-only treatment with no detrimental effect on the development of repeated fever or daily live weight gain. This suggests that NSAID alone may be a useful first-line treatment, provided adequate attention is given to ongoing monitoring to identify those cases that require additional antimicrobial treatment.

Introduction

Growth and development of healthy calves through the preweaning period is important both for ensuring longevity of the animals produced and to keep rearing costs at an economically viable price. A single case of pneumonia is estimated to cost £43 per dairy calf affected, with 47 per cent of UK dairy calves and 51 per cent of beef animals estimated to be affected (Esslemont and others 1998). The main costs are due to decreased growth rates (Wittum and others 1996), the cost of drug treatments (Schneider and others 2009) and mortality, which can range from 0.18 per cent to 3.9 per cent (Elliott and others 2014).

While early detection of calf pneumonia may improve treatment success and reduce infectious spread, the subtle signs associated with early disease (loss of appetite, depression or raised respiratory rate) are difficult to detect and often missed in the farm situation. Nasal discharge typically appears a median of 19 hours after fever develops, followed by a cough at a median of 65 hours after fever develops (Timsit and others 2011). This has resulted in recommendations to use detection of an undifferentiated fever for the initiation of treatment (Apley 2006), with the aim being to introduce therapy before the disease has progressed enough to cause clinical signs.

Many initial cases of pneumonia are primarily of viral aetiology (Tuncer and Yeşilbağ 2015) and are only complicated by later/secondary bacterial infection. However, calves are rarely identified at the initial viral stage, but are detected once the onset of signs associated with the secondary bacterial infection become established, resulting in a need for the use of antimicrobial treatment. NSAIDs have demonstrated efficacy in treatment of pneumonia when used in conjunction with antimicrobials due to their effects on reduction of lung consolidation (Lockwood and others 2003). However, no studies have assessed the use of NSAIDs as a stand-alone treatment. Therefore, a rationale for such a course of action could be that if detection is early enough in the course of the disease and the pneumonia of 'simple' viral aetiology, then the use of antimicrobials could be considered unnecessary.

To compound this message, there is an internationally recognised need to reduce antimicrobial usage, especially prophylactic and metaphylactic use, which has been common practice on calf-rearing units with pneumonia epidemics (Ives and Richeson 2015). Establishing treatment protocols that can reduce the use of antimicrobials is an important aspect of a veterinarian's role

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in the food-producing animal sector. Traditionally, poor observer sensitivity to clinical signs of pneumonia has resulted in treatments of animals whose initial acute pneumonia has progressed to a chronic suppurative form (Barrett 2000), resulting in a poor response to treatment, chronic weight loss and increased mortality rates (Breeze 1985).

The time-consuming nature of manual restraint and examination of rectal temperatures in calves invariably deters regular monitoring for fever in groups of calves. The use of formal calf health assessment protocols such as Wisconsin Calf Scoring have gone some way in helping to improve detection of sick calves (McGuirk and Peek 2014), along with development of technology. Infrared thermography scans, reticulorumen temperature boluses (Timsit and others 2011) and the Whisper stethoscope (Noffsinger and others 2014) have been trialled, but so far with limited application in the field. This study uses continuous real-time monitoring of calves through an affordable, novel, ear-canal temperature sensor (TempVerified FeverTags; Amarillo, Texas, USA). Each tag is a self-contained unit, made up of a temperature probe that is inserted deep into the external ear canal and a small circuit board with an LED light, which is secured in the pinna using a standard ear tag applicator.

This study aimed to use a randomised trial to directly compare the efficacy of NSAID therapy with antimicrobial therapy for the treatment of undifferentiated fever (presumed to be caused by pneumonia), with the fever defined as sustained ear canal temperature of ≥39.7°C detected by TempVerified FeverTags. We hypothesise that the use of an early NSAID treatment will reduce the requirement for antimicrobial usage as determined by resolution of the fever.

Materials and methods

A randomised positive control study design was used to compare the level of antimicrobial usage and growth rates between calves that were treated with an initial course of NSAID and an initial course of antimicrobial for fever. The trial protocol was approved by the Royal Veterinary College's Ethical Review Committee (URN 2015 1317) and granted a Veterinary Medicines Directorate Animal Test Certificate (ATC-S-057). A power calculation indicated that treatment group sizes of 48 would detect a 30 per cent difference in the proportion of calves requiring further treatment after 72 hours. Power was set at β=0.8, significance at $P \leq 0.05$.

Animals

Two Holstein dairy herds were recruited in the southwest of England. Both herds were closed, with vaccination for bovine diarrhoea virus (BVD), infectious bovine rhinotracheitis (IBR) and leptospirosis in use in the adult herd, and no vaccination in the calves. Calves were kept in large barns with a shared air space using natural ventilation, a range of ages from 0 to 16 weeks old and an all year-round calving pattern. Both farms fed the same milk replacer (20 per cent whey protein, 18.5 per cent fat, 8.3 per cent ash) made at 150 g/l, with farm 1 feeding 900 g/day through a group teat bucket and farm 2 feeding 800 g/day through an automatic milk machine. All calves had access to straw roughage and ad lib concentrates.

Calves were allocated to treatment groups by random number generation conducted by the author (SAM). Calves were enrolled if they developed fever related to respiratory disease between the ages of 0 and 10 weeks (preweaning calves). The origin of the fever was determined to be due to respiratory infection by exclusion of other common calf diseases (navel ill, joint ill, diarrhoea) through a structured protocol for physical examination carried out by the farmer, with training provided by the vet prior to the start of the study. Calves were removed from the study if they developed other diseases that required NSAID or antimicrobial therapy such as navel ill and joint ill. Calves that developed diarrhoea and were treated with oral electrolyte fluids (Life Aid, Norbrook Laboratories) were retained in the study unless they received additional NSAID or antimicrobial treatment (if deemed necessary through veterinary advice).

Fever detection

External ear canal temperature was measured as a proxy for core temperature every 15 minutes using a temperature probe that was inserted 5-cm deep into the external ear canal (TempVerified) (Fig 1). The FeverTags were preset by the manufacturer to be activated at a fever threshold of ≥39.7°C for a sustained period of six hours, upon which an LED light would flash for six hours to draw attention to the animal. The device would then enter a monitoring phase with the temperature taken every 15 minutes, and flashing would resume immediately if fever was detected again. Only one other study (McCorkell and others 2014) has used a similar temperature device, although this was an earlier model of the tag, which did not have the six-hour monitoring phase of the TempVerified model. The FeverTags used in this study had undergone quality-control testing as part of the manufacturing process and had demonstrated a temperature accuracy of ±0.1 per cent °F.

Treatment protocol

Calves were enrolled into one of two treatment groups: group 1 (NSAID) received flunixin meglumine (Allevinix, Merial) at 2 mg/kg via intramuscular injection daily for three consecutive days starting when the flashing tag was observed. If clinical signs of acute pneumonia developed after 24 hours (spontaneous coughing, severe nasal or ocular discharge, tachypnoea), or if the FeverTag was still flashing after 72 hours (indicating continued fever), calves were given gamithromycin (Zactran, Merial) at 6 mg/kg via a single subcutaneous injection. Group 2 (antimicrobial) received gamithromycin (Zactran, Merial) at 6 mg/kg via a single subcutaneous injection starting when the flashing tag was observed. If clinical signs of acute pneumonia developed after 24 hours, or the FeverTag was still flashing after 72 hours, then calves were given a NSAID treatment with flunixin meglumine (Allevinix, Merial) at 2 mg/kg via intramuscular injection daily for three consecutive days.

Fever for up to 72 hours following treatment without clinical disease was deemed tolerable as this allowed sufficient time for full therapeutic action and to prevent unnecessary secondary treatments. A repeat case of fever was defined as a temperature of ≥39.7°C for six hours, which was detected at least 10 days following the last treatment given for the initial case of fever. A 10-day duration was chosen as this is the licensed duration of action of Zactran in calves. Repeat cases of fever were treated using the same protocol as initial cases and recorded as a repeat case of fever within the statistics.

Calves were weighed at birth and weaning using a calf weigh scale (mechanical calf weighing crate, Bateman, UK). Further data on calf mortality and treatments given to the study animals was collected up to six months of age from the farm records.

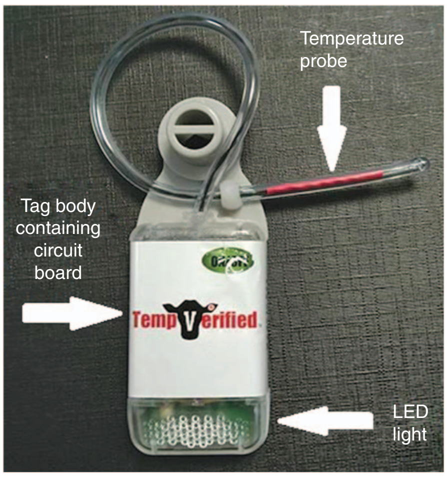

FIG 1: The TempVerified FeverTag consists of a temperature probe and casing to house the circuit board, battery and light emitting diode (LED) indicator light

Statistical analysis

Data were analysed using SPSS (SPSS V.21, Lead technologies 2012). Associations between the efficacy of each treatment group, the sex, the farm and the occurrence of diarrhoea was tested using multivariable binary logistic regression. Association between the treatment group and daily live weight gain was tested using analysis of variance (ANOVA). Associations between the requirement for a second treatment (continuation of fever 72 hours after the initial drug treatment) and sex, treatment group, farm and development of diarrhoea in the first two weeks of life was tested using multivariable binary logistic regression for calves that experienced an episode of fever. Kaplan-Meier survival analysis was used to assess the age at which respiratory disease-related fever was first detected.

Results

A total of 154 calves were enrolled into the study between May and October 2015 (Table 1) with 83 developing fever assumed to be related to respiratory disease. Eight calves were excluded due to fever detected by the FeverTag being caused by navel ill, and 12 calves were excluded due to development of diarrhoea, which required antimicrobial or NSAID treatment.

Of the 83/134 (61.9 per cent) calves with pneumonia-related fever, none developed acute signs of respiratory disease within 24 hours of being detected (such as severe tachypnoea), although mild coughing and nasal discharge was noted in some calves (although not formally recorded). Calves in treatment group 1 (NSAID) were five times more likely (P=0.002) to require additional treatment (antimicrobial) to resolve fever compared with group 2 (antimicrobial) who had a 64.7 per cent rate of resolution of fever (Table 2). However, 25.7 per cent of calves in group 1 did recover following NSAID treatment alone. Additional treatments (group 1 received additional antimicrobial and group 2 received additional NSAID) were administered after 72 hours in 42 (50.6 per cent) cases due to continued fever, with the binary logistic regression model (Table 2) indicating group 2 (antimicrobial) was less likely to require the second additional treatment (P=0.003).

The ANOVA indicated there was no significant difference in the daily live weight gain of the calves between the treatment groups (P=0.632), with a mean daily live weight gain of 0.64 kg/day (SE±0.02). No calves died while on the study, although, there was a 10 per cent mortality rate among the calves excluded from the study (2/20 excluded calves died). The Kaplan-Meier survival analysis (Fig 2) for time to development of the first fever experienced by preweaning calves produced a median age of 25 days (interquartile range 15–32 days).

For the postweaning period until six months of age, one calf died for unknown reasons (from group 2) and two calves required additional treatment for calf pneumonia (of which one calf was from group 1 and one was from group 2).

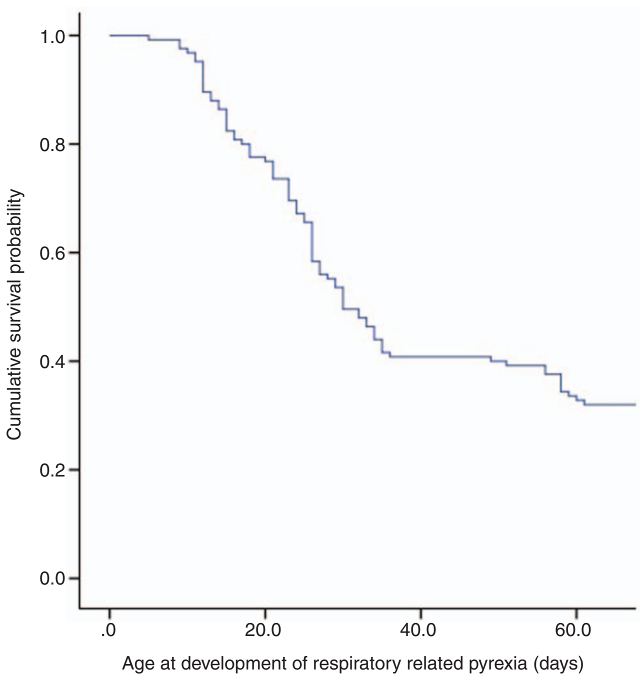

FIG 2: Kaplan–Meier survival analysis of the age (days) that respiratory disease-related fever developed in preweaning calves

TABLE 1: Total number of calves recruited into the trial and their division into the different treatment groups once fever had developed

	Farm 1	Farm 2
Total number of calves recruited	66	88
Calves that developed fever	43	40
Calves in treatment group 1 (NSAID)	21	20
Calves in treatment group 2 (antimicrobial)	22	20
Undifferentiated fever prevalence (%)	65.2	45.5
Calves excluded due to navel ill	2	6
Calves excluded due to diarrhoea	8	4

TABLE 2: The odds ratio and P values from the multivariable binary logistic regression for associations with the successful resolution of a case of undifferentiated fever with NSAID treatment, and the requirement for a second treatment 72 hours after the initial onset of fever was detected

Variable	Odds ratio for successful NSAID treatment (95% CI)	P value	Odds ratio for second treatment requirement (95% CI)	P value
Sex	0.47 (0.11 to 2.05)	0.31	2.31 (0.38 to 14.0)	0.36
Treatment group	5.09 (1.84 to 14.10)	0.002	0.16 (0.05 to 0.52)	0.003
Farm	0.24 (0.065 to 0.88)	0.031	4.78 (0.99 to 22.93)	0.050
Diarrhoea	0.42 (0.11 to 1.70)	0.22	1.03 (0.17 to 6.17)	0.98

CI, confidence interval

Discussion

This randomised clinical trial investigated the efficacy of NSAID-only treatment in comparison to antimicrobial therapy for undifferentiated fever in calves, which was considered to be due to pneumonia though a diagnosis of exclusion. The results indicate that using NSAIDs as the first-line treatment resulted in calves being five times more likely (P=0.002) to require an additional treatment (antimicrobials) to resolve fever compared with the use of antibiotics as the first-line treatment. However, the initial treatment group had no significant effect on the daily live weight gain or the prevalence of repeat fever episodes experienced by the calves. The early use of antimicrobials led to resolution of 64.7 per cent of the initial cases of pneumonia, compared with a 25.7 per cent success rate using a NSAID treatment alone (Table 2). Nonetheless, this study demonstrates the potential for reducing antimicrobial usage with NSAID initial treatment, as the delay in receiving the additional treatment of antimicrobials did not appear to have long-term detrimental effects on calf health up to six months of age.

There is a strong rationale for NSAID use in cases of pneumonia, primarily to reduce excessive inflammation associated with cell mediated immunity, cytokines and endotoxin release (Panciera and Confer 2010). One possible reason for the apparent lack of efficacy of NSAID-only treatment may be that the fever threshold used in this study (39.7°C) was too high. Other sources have indicated that the upper range for the normal body temperature of cattle is 39.2°C (Divers and Peek 2008), with a rectal temperature between 38.9°C and 39.4°C being given an abnormal classification (Lago and others 2006).

In addition to this, NSAIDs have an antifever nature; however, respiratory viruses have an optimal body temperature range for their survival, and the development of fever may actually be beneficial as part of the immune defence system (Apley 2006). This could mean that antipyretics are not an optimal treatment during preacute viral pneumonia infection.

Given the high success rate of the antimicrobial therapy in this study, it may support the hypothesis that bacterial infection had already become established at the time of treatment (Taylor and others 2010), resulting in an increased requirement of group 1 (NSAID) calves (39 per cent, $P<0.01$) to be treated with antimicrobial due to lack of resolution of fever. This was a major limitation of the study, with a lack of definitive diagnosis and pathogen identification. This would have allowed more robust conclusions to be drawn regarding the nature of the primary respiratory disease pathogens, especially given that the detection of pneumonia was primarily by development of fever. This pneumonia detection method is supported by Apley (2006) who concluded that in order to initiate early treatment, a presumptive diagnosis of pneumonia would often have to occur on the basis of depression and an undifferentiated fever. Combining the use of TempVerified FeverTags with other calf-monitoring tools such as the scoring system described by McGuirk and Peek (2014) may provide the most sensitive and specific method for the early detection and therefore treatment of calf pneumonia.

The overall period prevalence of pneumonia detected by this study was 61.9 per cent, which is higher than 47 per cent suggested by ADAS (2015), although this study selected the farms due their high-risk housing management. Both farms had calves housed in large shared air spaces, which can result in raised airborne bacterial levels, which also occurs with raised stocking densities (Lago and others 2006). Although the majority of airborne bacteria are non-pathogenic, they can provide an additional burden to the respiratory tract defences (Wathes and others 1983). The median age at which pneumonia was detected in this study was 25 days, which is in agreement with Elliott and others (2014) that indicated 53.7 per cent of pneumonia occurred in calves aged between two weeks and two months. This confirms that close monitoring of calves during this time period is important.

The eight calves excluded for developing navel ill all developed fever that was identified by the FeverTags, but only two of the 12 calves excluded for diarrhoea were detected as feverish. This indicates that the temperature monitors can be beneficial for detecting any calf disease that produces fever such as navel ill, with activation of the temperature monitors triggering a general clinical examination of a calf, therefore increasing detection rates of disease. This process for farmer-led calf examination demonstrated successful implementation of the protocol in this study, with the clinical exam and diagnosis carried out by a trained farmer. However, no confirmatory diagnostic tests were carried out and their abilities for correct disease classification were not formerly assessed. During this study, no cases of otitis or other ear infections were observed to be caused by the placement of the FeverTags, with only some mild inflammation noted around the FeverTag placement in the pinna, which would be expected during normal identification ear tag placement.

A significant advantage of the FeverTag temperature monitors in the study was the constant real-time monitoring of the calves' health status, aiding in early detection and therefore prompt initiation of treatment. In many conventional systems, continued monitoring of sick calves after treatment is challenging, leading to a further delay in the provision of secondary or repeat treatments for calves that continue to experience fever or progression of clinical symptoms. A total of 42 calves experienced continued fever following initial treatment, with further 23 calves having a repeat episode of fever, indicating the high requirement for continued monitoring of animals previously identified as sick.

Conclusion

Calf pneumonia is a costly disease affecting animals both in the dairy and beef industry, with long-lasting consequences on growth and productivity. The initiation of early treatment is important for reduction in lung pathology and stopping the progression of clinical signs.

The use of NSAIDs may be an important strategy for clinicians providing treatment and safeguarding welfare while withholding antimicrobial treatments for possible viral aetiologies. This treatment protocol, along with the use of early fever detection though FeverTags, enabled treatment to be administered much earlier in the disease course compared with that achievable on most 'manual examination' farms. We believe that this enabled an overall reduction in the total amount of antimicrobial treatments used when compared with a prophylactic antibiotic treatment strategy (a 30.1 per cent reduction in antimicrobial usage). This suggests the use of NSAIDs as a first-line treatment for early onset calf pneumonia as indicated by fever may be a suitable treatment protocol provided sufficient attention is given to continuous monitoring, and suitable consideration is given to the need for additional treatment with antimicrobials if the fever does not resolve.

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