Zeitschrift: Schweizer Archiv für Tierheilkunde SAT : die Fachzeitschrift für Tierärztinnen und Tierärzte = Archives Suisses de Médecine Vétérinaire ASMV : la revue professionnelle des vétérinaires

Herausgeber: Gesellschaft Schweizer Tierärztinnen und Tierärzte

Band: 141 (1999)

Heft: 4

Artikel: Efficacy evaluation of the use of oral tilmicosin in pneumonic calves

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DOI: https://doi.org/10.5169/seals-591464

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Efficacy evaluation of the use of oral tilmicosin in pneumonic calves

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Abstract

A trial was carried out on a beef cattle farm to obtain efficacy data for the treatment of naturally occuring bronchopneumonia in calves under commercial production conditions.The treatment was administered by medicating milk with three different tilmicosin doses mixed in the first 80% of the daily milk ration.
According to the clinical results, all three treatment regimens proved to be effective.The efficacies of the reduced dose of 12.5 mg tilmicosin/kg body weight daily for 5 days and of the reduced treatment duration with 25 mg/kg b.w. daily for 3 days were equivalent to a previously proven dose of 25 mg/kg b.w. daily for 5 days.

Key words: **tilmicosin – oral form – calf – bronchopneumonia – medicated milk**

Beurteilung der Wirksamkeit der oralen Tilmicosinanwendung bei Pneumonie-kranken Kälbern

Auf einem Kälbermastbetrieb wurde die Wirksamkeit der Behandlung der Kälber-Bronchopneumonie unter Praxisbedingungen untersucht. Die Behandlung erfolgte über medizinierte Milch mit drei verschiedenen Tilmicosindosierungen, die in den ersten 80% der täglichen Milchration verabreicht wurden.
Entsprechend der klinischen Resultate waren alle drei Behandlungen wirksam. Die Wirksamkeit der geringeren Dosierung mit täglich 12.5 mg Tilmicosin/kg Körpergewicht während 5 Tagen und diejenige der kürzeren Behandlungsdauer mit täglich 25 mg/kg KG während 3 Tagen waren äquivalent zur früher geprüften Dosis von täglich 25 mg/kg KG während 5 Tagen.

Schlüsselwörter: **Tilmicosin – orale Form – Kalb – Bronchopneumonie – Medizinalmilch**

Introduction

Tilmicosin is a new macrolide antibiotic shown to be effective in the parenteral treatment of respiratory diseases in young calves and with specific activity against *Pasteurella haemolytica* serotype A1 and *Mycoplasma* spp. (Gourlay et al., 1989; Thomas et al., 1996; Sustronck et al., 1997; Rizet et al., 1997).
Recent field experiments in Europe, using the oral form of tilmicosin fed via milk replacer at 12.5 mg/kg twice daily for 5 days, have confirmed the efficacy of this dosage regimen in pneumonic calves (Thomas et al., 1996; Peters et al., 1997; Reeve-Johnson et al., 1997). Pharmacokinetic data from treated calves revealed lung concentrations which exceeded the average minimum inhibitory concentrations (MICs) for pathogenic Pasteurella species by 3 to 4 times (Peters et al., 1997; Reeve-Johnson et al., 1997).
The objective of the present study was to obtain efficacy data for the treatment of bronchopneumonia in calves under commercial production conditions, by giving medicated milk with 3 different tilmicosin treatment regimens.The daily dose of 25 mg/kg body weight for 5 days was compared with a reduced daily dose (12.5 mg/kg for 5 days) and a reduced treatment duration (25 mg/kg daily for 3 days).

Animals, materials and methods

Animals and animal management

In order to accumulate sufficient cases, the field trial was conducted in three parts on the same beef cattle farm under the same husbandry conditions.
Altogether, 70 from 84 milk fed male calves fell spontaneously ill. Forty-eight calves of approximately 4 weeks of age and an average body weight of 70 kg were used for the trial. The breeds were Simmental, Brown Swiss, Red Holstein, Blonde d'Aquitaine, Holstein Friesian and cross-breeds of these breeds. Upon arrival each calf was identified by a numbered plastic eartag and transponder belt. The calves were housed in a separated calf rearing stable with enough space for 80 calves. They were kept free on a deep straw-litter with a compartment equipped with a milk replacer machine for individual feeding of animals. All animals remained there together in one group until the end of each trial part.
All calves were fed a non medicated commercially available milk replacer individually by an automatic milk dispenser. The volume of each single dose of the milk replacer was standardised to 0.5 l. The computer program distributed the daily milk ration according to the feeding plan over the whole day. In addition to the milk replacer, water, a pelleted concentrate, corn silage and hay were available *ad libitum.*

Inclusion criteria

From arrival each calf was examined twice daily to detect diseased calves. Inclusion criteria were the clinical diagnosis of pneumonia comprising 1. both the demeanour and respiratory scores being 1 or more (Table 1a and 1b) and 2. rectal temperature being 39.5 °C or above.

Treatment

Upon diagnosis of respiratory disease, each calf was randomly assigned to one of the three treatments shown in Table 2. The trial period lasted 15 days for each calf and consisted of three phases:
1) 3- or 5-day medications,
2) 7- or 5-day twice daily observation until day 10,
3) 5 days monitoring for relapses.
Pneumonic calves received the treatment in the first 80% of the daily available milk ration. The remaining 20% were not medicated. The total daily milk replacer consumption was recorded individually as animals were equipped with transponder belts.
The product tested was an aqueous concentrate of tilmicosin with a concentration of 250 mg tilmicosin/ml.

Measurements and records

The following criteria were recorded for each animal: milk replacer intake, body weight at arrival and at the end of trial (on day 15), demeanour and respiratory scoring from day of arrival until the end of trial (twice daily, morning and evening), rectal temperature (taken twice daily after demeanour and respiratory scorings, morning and evening), presence/absence of cough, nasal or ocular discharges, or diarrhoea, and presence/absence of other diseases than pneumonia.
From the beginning of each trial part, the veterinary personnel scored all the animals twice daily at the same times each day (i. e. beginning at 7 a.m. and at 5.30 p.m.) and recorded the clinical data on a daily work sheet. Once a calf had fulfilled the inclusion criteria, the owner of the site was informed and he programmed the medication after the clinical scoring in the computer of the automatic milk dispenser, without informing the vete-

Table 1a: Demeanour score

Score	Demeanour	Description
0	normal	alert calf, responds to presence of observer, ears pricked
1	subdued	response decreased, not as 0, but alert
2	apathy	ears turned down, coat losing lustre, less responsive to observer, not totally inappetant
3	marked depression	failure to respond to observer, hunched stance, may be inappetant
4	moribund	total inappetance, no response to observer, euthanized on grounds of animal welfare, due to severity of symptoms

Table 1b: Respiratory score

Score	Respiration	Breaths per minute
0	normal	< 35
1	slightly increased rate on careful observation	35–49
2	obviously increased rate	50–60
3	tachypnoea	> 60

Table 2: Treatment regimens

Group	Treatment
25*5	25 mg tilmicosin/kg body weight a day for 5 consecutive days
25*3	25 mg tilmicosin/kg body weight a day for 3 consecutive days
12.5*5	12.5 mg tilmicosin/kg body weight a day for 5 consecutive days

rinary personnel which treatment this calf was receiving. Fifteen days after the beginning of medication, the clinical examination was finished.
If a necropsy was performed, pathological and bacteriological examinations from the lung were carried out.

Evaluation of the results

The results were evaluated on the basis of clinical recovery, recovery period, relapse incidence and incidental mortality. Clinical recovery is defined as the proportion of animals which have responded to the treatment. Animals were considered recovered if the rectal temperature was < 39.5 °C and the respiratory and demeanour scores had decreased from day 0 for 2 consecutive examinations. The recovery period is the shortest period between day 0 and the time point, when clinical recovery as defined as above, is attained.
All post-mortem examinations were performed by the personnel of the Institute of Veterinary Pathology and the Institute of Veterinary Bacteriology of the University of Zurich within 6 hours after death.

Statistics

Categorical data, e.g. the number of sick animals, were evaluated using a chi-square test or Fisher's Exact test if there were small expected counts. Quantitative data, e.g. weights and mean scores, were assessed by analysis of variance, which included terms for block (trial parts) and treatment. The p-values were calculated for overall tests for differences between the three treatment groups.

Results

The data of 48 calves was evaluated: 17 calves in treatment group 25*5, 16 in group 25*3, and 15 in group 12.5*5. The treatment groups were well balanced with respect to initial body weight (Table 3). Ten calves (20.8%) fell ill on day 1 and 2, and 26 calves (54.2%) fell ill on days 4–6 (Figure 1).

Clinical data

An overview over the clinical data is presented in Table 3. All but 4 animals recovered clinically by day 5, and only 1 animal treated with 25 mg/kg for 5 days (treatment group 25*5) had not recovered by day 10. By day 15, all calves recovered. The average recovery period was 3.5 days for treatment group 25*5 and 2.3 days for each of the other two groups. Ten animals relapsed by day 10 (2 in treatment group 25*3, 4 in each of the 2 other groups), and 14 calves relapsed by day 15. Relapse occurred on day 7.5 on average in treatment group 25*5, and on day 8 on average in each of the two other groups. There were no statistically significant differences between the three groups in terms of the day of recovery and relapse incidence.
The mean daily weight gain was significantly higher in treatment group 12.5*5 than in the other two groups, although it should be noted that one animal in this lower dose group had a particularly high value (1467 g/day). The majority of animals refused feed during the first five days, and the average percentage intake was similar across the three treatment groups. The percentage feed intake improved during the study, and was over 90%, on

Table 3: Efficacy of oral tilmicosin (n = 48)

Parameter	Treatment group			P-value
	25*5	25*3	12.5*5	
Number of animals	17	16	15	
Initial body weight (kg)	73.47	74.94	75.00	NS
Daily weight gain (g)	372	404	566	< 0.05
Recovered by day 5	15	14	14	NS
by day 10	16	16	15	NS
Day of recovery	3.5	2.3	2.3	NS
Relapsed days 1–5	1	1	0	NS
days 6–10	3	1	4	NS
days 11–15	1	2	1	NS
Refused feed days 1–5	14	11	13	NS
days 6–10	10	8	8	NS
Milk intake days 1–5 (l/d)	5.65	5.83	5.39	NS
days 6–10 (l/d)	6.48	6.27	6.43	NS
Demeanour score: initial mean	1.03	1.22	1.00	NS
mean days 1–2	0.72	0.35	0.37	< 0.01
mean days 3–5	0.24	0.37	0.25	NS
mean days 6–10	0.25	0.14	0.18	NS
Respiratory score: initial mean	1.44	1.55	1.19	NS
mean days 1–2	0.69	0.50	0.50	NS
mean days 3–5	0.31	0.28	0.26	NS
mean days 6–10	0.27	0.24	0.18	NS
Temperature: initial mean (°C)	40.16	39.83	40.04	NS
mean days 1–2 (°C)	39.65	39.35	39.46	NS
mean days 3–5 (°C)	39.10	39.02	39.11	NS
mean days 6–10 (°C)	39.03	38.97	39.04	NS

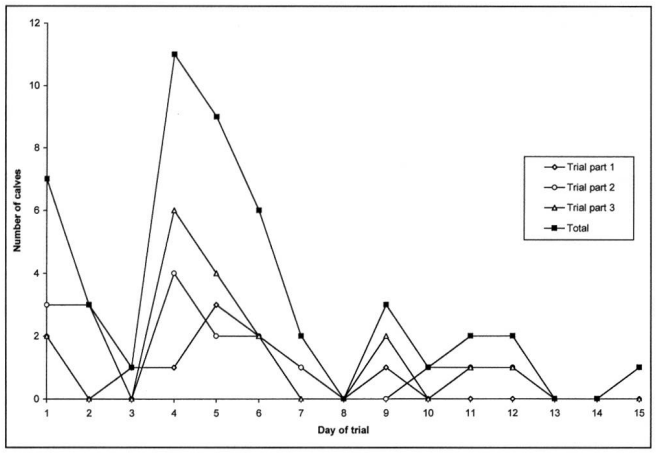

Figure 1: Day of illness

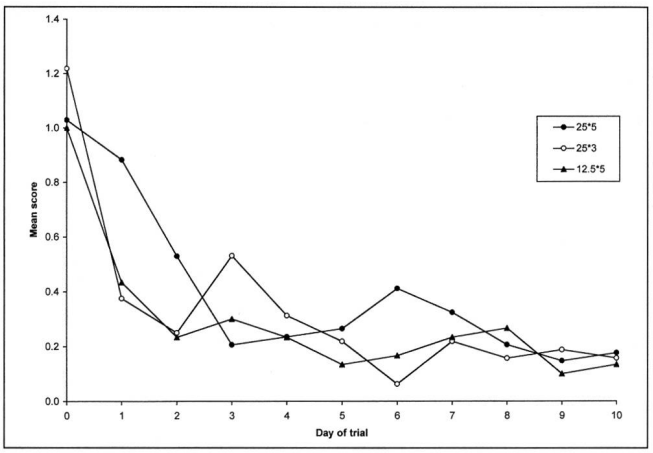

Figure 3: Mean demeanour score

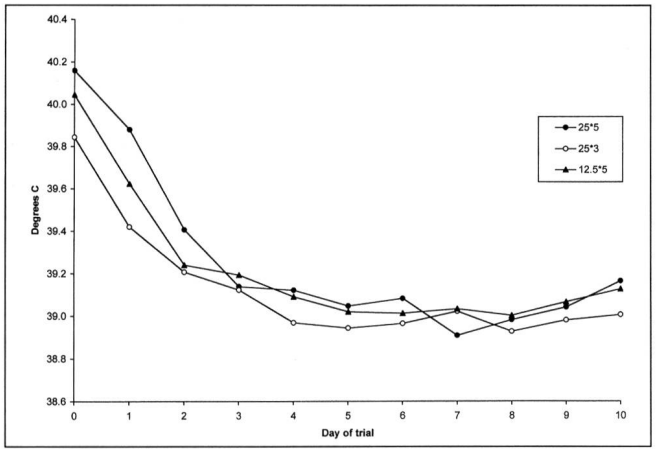

Figure 2: Mean temperature

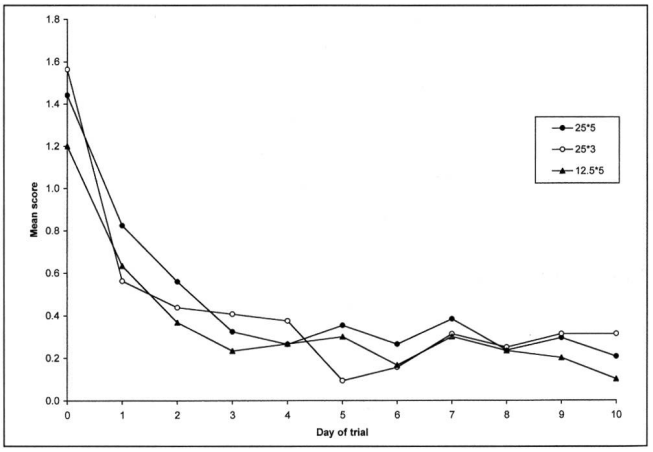

Figure 4: Mean respiratory score

average, in each treatment group during days 6 to 10.
All three treatments lowered temperatures, demeanour scores and respiration scores within 24 hours (Figures 2–4). There were some differences between the treatment groups during days 1–2, with demeanour scores, respiratory scores and temperatures being generally higher in treatment group 25*5, but there were no other statistically significant differences between the groups in terms of these three parameters.
Incidence of cough, discharge and diarrhoea was generally similar in the three treatment groups and showed little change during the 10 days of the study. The number of animals with diarrhoea during days 1–2 was significantly higher in the lowest dose group, but there were no other statistically significant differences between the groups in terms of these parameters. Diarrhoea was observed in several calves of all treatment groups and in not treated animals, too. In feces samples *Campylobacter jejuni* and *Campylobacter coli* were isolated.

Post-mortem examinations

No animal died in the course of the trial. However, one calf out of treatment group 25*5 was euthanized because of severe dehydratation as a result of never drinking the daily milk ration. The right cranial lung lobe and the cranial part of the middle lung lobe were completely haemorrhagic and consolidated. In the section, multiple consolidated nodules were observed. The histological examination showed a severe bronchointerstitial pneumonia.
The bacteriological examination showed ++/+++ *Arcanobacterium pyogenes,* + *E. coli,* + *Proteus vulgaris,* + *Streptococcus suis,* type 1 and no Mycoplasma. The minimum inhibitory concentration (MIC) for tilmicosin of the bacteria isolated was 2 µg/ml for *Arcanobacterium pyogenes* and > 32 µg/ml for the other three species.

Discussion and conclusions

Oral medication can have a number of advantages especially in situations where rapid control of disease problems are required in groups of animals. Additional advantages include less requirements to handle animals with consequent decreases in labour costs and stress to animals.
Tilmicosin even in low concentration showed very good antibacterial activity against several Gram-positive and

some Gram-negative bacteria which are involved in the pathogenesis of pneumonia (Reeve-Johnson et al., 1997). Tilmicosin having a fast peak in the plasma and a high and prolonged concentration in the lungs is an outstanding antibiotic for treating pneumonic calves (Peters et al., 1997). Tilmicosin showed to provide good protection against intra-tracheal inoculation of calves with *Mycoplasma bovis* and *Pasteurella haemolytica,* type A1, compared with untreated calves (Gourlay et al., 1989; Thomas et al., 1996; Reeve-Johnson et al., 1997; Sustronck et al., 1997).

In the present experiment the oral tilmicosin solution proved to be effective for the treatment of calf pneumonic diseases. The clinical responses of the reduced treatment duration with 25 mg tilmicosin/kg body weight daily for 3 days and the reduced dose level with 12.5 mg/kg daily for 5 days proved to be as effective as the proven dose of 25 mg/kg daily for 5 days.

There were no statistically significant differences between the three groups in terms of the day of recovery, relapse incidence, initial body weight and milk intake. The mean daily weight gain was significantly higher in the lower dose group because of a particularly high value of one animal. During days 1–2, the demeanour scores, respiratory scores and temperatures were generally higher in the group treated with the proven dose, but there were no other statistically significant differences. The incidence of cough and discharge was generally similar.

The observed diarrhoea occured in all treatment groups and even in not treated animals. Because *Campylobacter* spp. were isolated, the etiology of diarrhoea seemed to be infectious.

One fifth (20.8%) of the calves fell ill with symptoms of respiratory tract diseases on day 1 and 2, and 54.2% on days 4–6, respectively. This high morbidity of the calves after arrival seems to point out that a routine use of antibiotics for prophylactic use is reasonable.

Acknowledgments

This study was financially supported by Elanco, European Research & Development, Basingstoke, UK. For assisting in the clinical scoring of the calves, we thank the students of the Veterinary Hospital. Particular thanks also to Mr. H. Schibli, Otelfingen, for making his beef cattle site available for this study and to the personnel of the Institute of Veterinary Bacteriology and of the Institute of Veterinary Pathology for the fecal analysis and the post-mortem examinations.

Evaluation de l'éfficacité de l'utilisation de la tilmicosine par voie orale chez des veaux atteints de pneumonie

Un essai a été effectué dans une exploitatin d'engraissement pour obtenir, dans des conditions de production commerciale, des données sur l'efficacité du traitement de la bronchopneumonie des veaux contractée par voie naturelle. Le traitement a été administré par lait médicamenteux au moyen de trois doses de timilcosine mélangées avec la première portion de 80% de la ration journalière de lait.

Selon les résultats cliniques, les trois régimes de traitement ont été éfficaces. L'efficacité de la dose journalière réduite de 12.5 mg de tilmicosine par kg de poids corporel pendant 5 jours ou du traitement d'une durée réduite avec 25 mg/kg/jour pendant 3 jours était équivalente à la dose de 25 mg/kg/jour pendant 5 jours dont l'éfficacité a été démontrée auparavant.

Valutazione dell'efficacia dell'uso orale di tilmicosin in vitelli ammalati di polmonite

È stato eseguito uno studio in un allevamento di manzi, per ottenere dati sull'efficacia del trattamento con tilmicosin contro la broncopolmonite in vitelli tenuti sotto condizioni produttive commerciali. Il trattamento degli animali avveniva con la somministrazione di tre dosaggi differenti di tilmicosin mescolato con il primo 80% della razione giornaliera di latte.

Dai risultati clinici risulta che tutti e tre i dosaggi erano efficaci. L'efficacia della dose ridotta di 12.5 mg/kg di peso corporeo per giorno durante 5 giorni et il trattamento con 25 mg/kg giornalieri limitato però a tre giorni consecutivi era equivalente alla dose precedentemente risulta effettiva di 25 mg/kg per giorno durante 5 giorni.

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Manuskripteingang: 4. August 1998
in vorliegender Form angenommen: 7. Oktober 1998