

Paper

Comparing the curative efficacy of topical treatment with thiamphenicol and oxytetracycline on digital dermatitis lesions in dairy cattle

M. Holzhauer, R. Ploegmakers-van Deventer, D. Smits, W. Swart

The efficacy of two topically applied antibiotics for the treatment of painful ulcerative stage of bovine digital dermatitis (BDD) lesions was compared in a clinical trial conducted on five dairy farms in the Netherlands during the autumn of 2015. A total of 109 cows with an ulcerative (M2) stage of BDD were randomly appointed a treatment with an antibiotic-based spray. One treatment contained thiamphenicol as active ingredient (TAF). The other treatment had oxytetracycline as active ingredient (ENG). The experimental unit for this study was the hind claw with the presence of an ulcerative BDD lesion. On day 0, claws with ulcerative BDD lesions were trimmed, cleaned, photographed and thereafter treated randomly either with TAF or ENG. Cure was defined as the transition of an ulcerative lesion into a non-painful chronic (M4) or into a healed (M0) stage of BDD at day 28 post-treatment. The cure rate at day 28 of M2 BDD lesions treated with TAF was 89 per cent (95 per cent CI 0.78 to 0.94), and for ENG 75 per cent (95 per cent CI 0.67 to 0.86). So the difference in cure rate was 14 per cent (95 per cent CI 0.00 to 0.27), which was statistically significant. The P value in this experiment is very close to 0.05 indicating that the effect is quite small. If a two-sided test would be used, the small significant effect, in this experiment, will disappear. Overall, the significant better curative effect of TAF on BDD M2 lesions was small, compared with ENG.

Introduction

Lameness in dairy cattle is mainly caused by claw disorders (Bergsten and Frank 1996) which have either an infectious or a non-infectious cause. The most important infectious claw disorder is digital dermatitis (DD) with an estimated prevalence of > 90% and > 20% in the Netherlands in 2006 at herd and cow level respectively (Holzhauer and others 2006). Infection with *Treponema* spp is considered the main causative factor of the typical plantar skin lesions (Evans and others 2011). The DD lesions can be divided into different stages (M0 to M4) depending on the severity and the reaction on palpation of the lesions as proposed by Döpfer and others (1997) and modified by Holzhauer and others (2008). The ulcerative stage (M2) is both very painful and infectious (Mumba and others 1999)

To reduce the consequences of this very painful condition, (Blowey and Sharp 1988; Evans and others 2008; Buijnis and

others 2012) different management strategies have been developed (see: <http://www.delvalcorporate.com/milk-matters/the-farm/five-point-plan-for-control-of-digital-dermatitis/>). A main point of the plan is prompt treatment of the M2 lesions (Barker and others 2009). Topical treatment with different active substances (antibiotics and non-antibiotics) has proven to be very effective in various studies: Laven and Hunt (2001) studied the effect of two topical antibiotic sprays (valnemulin and lincomycin), Holzhauer and others (2012) studied the effect of zinc and copper chelates, and Kofler and others (2015) studied the effect of salicylic acid for treatment of DD in dairy cows.

Currently, the only registered antibiotic treatment of DD in the Netherlands is topical treatment with antibiotics of the tetracyclin group; this therapeutic treatment is widely applied amongst West-European claw trimmers. However, from the perspective of antimicrobial sensitivity, it would be preferable if other therapeutics based on different antimicrobial mechanisms became available.

The objective of this study was to evaluate the therapeutic effect (cure rate) of a new topical antibiotic treatment with thiamphenicol as active substance in comparison with oxytetracyclin on painful M2 DD lesions. Still, topical application of antibiotics - usually chlor- or oxytetracyclin - is the most widely applied therapeutic treatment amongst West-European claw trimmers (Holzhauer, personal communication). Although topical treatment has the advantage of limited antibiotic usage and it also fulfills the requirements of legislation, this should be

Veterinary Record (2017)

doi: 10.1136/vr.103758

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Provenance: not commissioned;
externally peer reviewed

Accepted March 4, 2017

optimized. The availability of different antibiotics for treatment is preferable to reduce the risk for induction of antimicrobial resistance. The objective of this study was to evaluate the therapeutic effect (cure rate) of a new topical antibiotic treatment with thiamphenicol as active substance in comparison with oxytetracyclin on painful M2 DD lesions.

Materials and methods

Herd management

The trial was conducted on five commercial dairy farms in the centre of The Netherlands (Table 1), which all participated in regular routine claw trimming programmes. Based on the sample size estimation (see later) and to be able to perform the study on a limited (5) number of herds, selection criteria for participation of dairy farms were as follows: a BDD prevalence >20 per cent with a minimum of 20 cows with M2 BDD lesions per farm, as assessed during previous claw trimmings; a free stall with slatted floors; and a guarantee not to use footbaths from two weeks before and during the four weeks research period. The (non-) lactating cows and heifers with M2 BDD lesions on one or two hind feet detected at the start visits were included in the trial. The total number of cows selected for the start of the trial was 109 and contained 137 hind feet with appropriate lesions.

Study design and treatments

In this clinical field trial, the efficacy (i.e. cure rate) of thiamphenicol (TAF SPRAY, Dechra Veterinary Products; MAH Eurovet Animal Health B.V., Bladel, The Netherlands; abbreviated as TAF) and oxytetracycline (Engemycin Spray, MSD B.V. Boxmeer, The Netherlands, abbreviated as ENG) in the treatment of M2 BDD lesions was determined and compared. Both sprays are officially registered veterinary products. A positive control was chosen for animal welfare reasons as not to deny animals treatment of the painful M2 stage of BDD.

All BDD lesions included in the trial were dry cleaned, macroscopically classified, trimmed and photographed at D0 and D28. Classification of BDD was performed according to a standardised scoring system comprising five stages (M0–M4) as developed by Döpfer and others (1997). According to this scoring system, M0 is recorded for feet with normal digital skin where BDD is absent during macroscopic inspection (Fig 1a), M1 is the early-stage lesion (0–2 cm) that is not painful; M2 is the classical ulcerative stage with a diameter ≥ 2 cm that is often painful upon touch (Fig 1b); M3 is the healing stage when the lesion is covered by a scab; M4 is the chronic stage characterised by dyskeratosis or proliferation of the surface that is generally not painful (Fig 1c) and M4.1 are a combination of chronic lesions with indication for reactivation. If different stages of BDD were present, the claw was typified according to the most prominent stage of the lesion. Besides scoring of the lesions, attention was paid to the presence of adverse reactions or side

effects, with specific attention for redness and swelling of the treated skin. To minimise impact on animal welfare in this study, it was decided to compare the product to be investigated (TAF) with another registered product (ENG), instead of a control group without any treatment.

On D0, the first M2 lesion in a herd that was found was assigned to treatment group A or B according to a list of random chosen treatments determined beforehand, based on the random generator of Microsoft Excel (2010). In group A, TAF was applied according to the Summary of Product Characteristics of the Producer (SPC) which includes spraying for three seconds from a 15–20 cm distance and repeated for two consecutive days. In group B, ENG was applied exactly as TAF spray and according to the same timeframe (Fig 2).

The sample size was calculated to be able to detect a 20 per cent difference between the estimated cure rate of ENG in previous studies (60 per cent; Holzhauser and others 2008) and of the presumed cure rate of TAF (80 per cent) with 95 per cent confidence and 80 per cent power, neglecting the effect of clustering within herds. Based on these assumptions, a sample size of 50 hind claws with M2 lesions in each group was needed.



FIG 1: (a) M0 lesion; (b) M2 lesion and (c) M4 lesion. Different stages of bovine digital dermatitis lesions.

TABLE 1: Information of the five participating dairy herds in the clinical trial and the distribution of participating cows over the herds (n=137)

Herd	Start trial	End trial	Cows herd, n	Cows trial, n	Hind claws trial, n	Hind claws evaluated, n
1	August 31, 2015	September 28, 2015	161	31	35	34
2	September 7, 2015	October 5, 2015	87	16	22	22
3	September 8, 2015	October 6, 2015	90	17	21	19
4	September 9, 2015	October 7, 2015	75	25	33	30
5	September 14, 2015	October 12, 2015	207	20	26	24
				109	137	129

D0	D1	D2	D7	D14	D28
Treatment	Treatment	Treatment	Evaluation	Evaluation	Evaluation
Evaluation					

FIG 2 : Timeframe for the treatment and evaluation of the M2 bovine digital dermatitis lesions.

To guarantee uniformity in scoring, all recordings were performed by two veterinarians, in which the first scoring (D0) at the first herd was performed together for standardisation. All hind claws with M2 lesions on D0 were photographed on D0 and D28 for objective evaluation afterwards. All treatments were conducted by a professional claw trimmer. Both treatment and scoring were executed at the time the cow was standing in a chute for trimming. At D28, the original treatments could not be traced, so was blinded as to ensure that the evaluation is done fairly. No (walk-through) foot baths or other treatments were applied in the two weeks before the start of the trial and during the total trial period.

Daily evaluations were performed by the dairy farmer for presence of painful lesions. In case of necessary extra treatments, as discussed with the dairy farmers in advance, these were always executed with the chosen trial product. This meant for both the case and the control group a registered product for treatment of DD. At D7 and D14, an extra control was performed by the researchers while cows were standing in the milking parlour or at the feeding rake. As discussed in advance of the study, in case of any doubt it was possible to contact the researchers or the local veterinarian. These cows were considered not to be cured. Cows that were treated with antibiotics for other reasons during the trial (e.g. mastitis) were excluded from the trial, as well as the cows that were not present at D28.

Statistical analysis

The experimental unit was a hind claw with a M2 BDD lesion. Cure in this study was defined as the transition of M2 BDD into a healed (M0) or non-painful chronic stage (M4) at D28. The healing to M0 was also analysed separately. A Wilcoxon rank-sum test was used to compare the proportions of cured M2 lesions for the different treatment groups for parity and days in milk as lower parity and first part of lactation are estimated as risk factors in previous studies the results might be influenced by these criteria (Argáez-Rodríguez and others 1997, Read and Walker 1998, Holzhauer and others 2006).

Data were analysed in STATA/SE V. 14.0, 28 days after the initial treatment with TAF or with ENG (P value <0.05). A Fisher exact test was used to compare the cure rate of TAF with ENG both for each herd separately and for comparing the overall crude risk rate (RR). The overall RR was finally corrected for the effect of herds, by applying the Mantel-Haenszel test.

Results

In total, 129 hind feet, divided over 102 cows, were treated and evaluated on D0 and D28. This differs from the total number at the start of the trial because eight units (i.e. hind claws, three treated with TAF and five with ENG) were excluded from the study because the protocol could not be fully executed. The reasons were

the absence of M2 lesion to be treated for the claw trimmer at D3 (3×), not correct treatable at D1 due to tricky nature of the cow (1×), cows been removed from the farm/culled (3×) and cows escaping from the stable into pasture during scoring on D28 (1×). After correction for loss of data of cows, the data consisted of 61 hind claws treated with TAF and 68 hind claws treated with ENG to be used for analysis. The distribution of the hind claws over the five herds was respectively 34, 22, 19, 30 and 24.

There was no significant difference between the age distribution of the TAF and the ENG group ($p = 0.55$). This indicates that in this study age did not have an effect on the relation between TAF and ENG and the corresponding cure rates.

Based on the transition to M0 or M4, the M2 BDD cure rates at D28 of TAF and ENG are determined and displayed in Table 2. The cure rate of M2 BDD lesions treated with TAF was 89 per cent (95 per cent CI 0.78 to 0.94) and with ENG 75 per cent (95 per cent CI 0.67 to 0.86), indicating a risk difference of 14 per cent (95 per cent CI 0.00 to 0.27), and the crude RR was 1.18 (95 per cent CI 1.00 to 1.39). If a two-sided test would be used, the small significant effect, in this experiment, will disappear. The transition to M0 separately showed no statistical difference.

The Mantel-Haenszel RR, which corrects for possible differences due to herds, was 1.19 (95 per cent CI 1.01 to 1.41). This value is not much different from the crude RR of 1.18, indicating that there was no significant herd effect. The RR per herd was more than unity for TAF over ENG (four out of five herds) and differed statistically significant in one out of five herds (Table 2, herd 2). On day 7, all M2 (from day 0) had become non-M2 for TAF compared with two remained M2 for ENG.

Discussion

The objective of this study was to determine the curative effect of a new antibiotic spray for treatment of ulcerative DD lesions in comparison with another registered product. Based on definitions presented in the paper, cure rates of 89 per cent and 75 per cent were estimated for TAF and ENG, respectively. In other studies with topical antibiotic treatments, cure rates at D30 around 60–70 per cent were found, except the study of Shearer and Hernandez (2000) and Laven and Hunt (2001), who estimated at day 14 cure rates of 28 per cent and 40 per cent, respectively, but besides differences in active components, strategies of application (e.g. daily application) and days of evaluation were different also which might have influenced the final result and therefore studies remain hard to compare. In our opinion, it is economically more effective to apply antibiotics intensively for a short period than for a longer period and the last strategy results nowadays in more opposite from the public also.

In a more recent study, a comparison was made between tetracycline hydrochloride in a paste and as a powdered form of tetracycline hydrochloride held in place by a bandage. In this

TABLE 2: Number of claws with M2 bovine digital dermatitis lesions treated with ENG and TAF and cured to M0 or M4 at D28, the cure rate and the difference in cure rate related to TAF overall and for the different herds

	ENG treated, n	ENG M2 cured*	Cure rate ENG	TAF treated	TAF M2 cured	Cure rate TAF	Cure rate difference	P value (Fisher exact test)
Herd 1	9	8	0.89	10	8	0.80	0.09	0.542
Herd 2	22	18	0.82	9	9	1.00	-0.18	0.232
Herd 3	11	6	0.55	13	12	0.92	-0.38	0.048
Herd 4	14	12	0.86	19	17	0.89	-0.04	0.574
Herd 5	12	7	0.58	10	8	0.80	-0.22	0.268
Total	68	51	0.75	61	54	0.89	-0.14	0.039

*Cured means transmission from M2 into M4 or M0

study, 47.4 per cent and 57.1 per cent were healed at 8–12 days post-treatment, respectively (Cutler and others 2013). These treatments have a much lower cure rate than the 75 per cent cure rate of with topical treatment with oxytetracycline in this study. In those and other studies, it is not completely clear what was the definition of cure and at different other point's studies are not standardised. A potential reason for our better cure rate might be the three consecutive treatment days as compared with other studies, which applied only once (Shearer and Hernandez (2000), Berry and others 2010). Also our cure rate of ENG might be impacted by the fact that ENG was applied identical to TAF. This means spraying for three seconds instead of one to two seconds according to the product label of ENG. On the other hand, according to the SPC ENG should be sprayed twice a day while in this study this is done only once a day. It is possible that application twice a day might have resulted in a better cure rate for an oxytetracycline-based spray.

Data presented in this study indicated a cure rate of TAF at D28 after the start of treatment of 89 per cent (Table 2), which is better compared with the cure rates of antibiotic treatments in other studies. In other recent studies, investigators tested non-antibiotic products such as copper and zinc chelate (Holzhauer and others 2012) and salicylic acid (Fiedler and others 2015, Kofler and others (2015)). Results of these studies were more in line with our results: in the 2012 Dutch study, cure rates of 92 per cent were scored at D28 and in the Austrian study 76 per cent pain-free at D21. However, cure rates are also influenced by different other factors (e.g. production level of cows, cleanliness of floors, ratio number of cows/cubicles, correct size of the cubicles), and therefore it is important to have a control group within the same herd.

It is reported that at a later stage some M2 lesions can reoccur, where it is hard to determine if it is reinfection or reoccurrence of a non-healed lesion (Berry and others 2010). More detailed insight could have been obtained by good scoring and analysing of D7 and D14 data, but in this study these data were collected while cows were in the herd and milking parlour and not in a trimming chute and are therefore not included in the results.

For reasons of practical feasibility, no permission of dairy farmers in this regular herds and for financial reasons, no biopsies were taken for further histopathological investigation of the lesions in this study.

Remarkable observation at D28 was that the complete cure to M0 seems to be also influenced by herd-specific factors (especially for TAF), where in two herds most hind claws were scored as M0 and in two other herds almost all cured cows were scored as M4. Because of the small number of herds, the data were not shown. The reason for this difference is not completely understood, but might be related to local circumstances and as mentioned before explain differences between studies. In the herds with most M0 cows were pastured, while in the 'M4 herds' cows were housed permanently.

Conclusion

The use of topical TAF Spray for three consecutive days showed a small significantly better treatment of the painful ulcerative stage of BDD compared with three consecutive days of topical treatment with Engemycin Spray.

Ethical approval

The study has been presented on beforehand of, during and afterwards the study to the GD Animal Welfare Committee to guarantee prevention of any possible affection of animal welfare.

Acknowledgements

The authors like to acknowledge the participation and assistance of the dairy farmers and the claw trimmers of AB-Oost for their patience and accurate trimming of the dairy cows.

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Veterinary Record published online May 2, 2017

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