PEER REVIEWED

Efficacy of an Internal Teat Sealer Used in Conjunction with Intramammary Antibiotics on the Cure of Intramammary Infections during the Dry Period

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Abstract

The objective of this study was to determine if an internal teat sealer used in addition to dry-cow antibiotics would have a beneficial effect on the elimination of intramammary pathogens during the dry period. In total, data from 425 culture-positive quarters from 270 Holstein-Friesian dairy cows were utilized in this trial. Milk samples were collected aseptically two weeks prior to the anticipated dry-off date, on the dry-off date and again at 1-8 days-in-milk. Infected quarters were randomly assigned to treatment with both an internal teat sealer and a dry-cow antibiotic, or a dry-cow antibiotic alone. Quarters were defined as cured if the pathogen(s) isolated in the dry-off sample were not isolated in the postpartum sample. There was no difference in overall bacteriological cure between the two treatment groups, internal teat sealer and dry-cow antibiotic versus dry-cow antibiotic alone. Similarly, no significant differences were observed for cure of either major or minor pathogen infections.

Résumé

L'objectif de cette étude était de déterminer si l'utilisation conjointe d'un scellant à trayons intramammaire avec des antibiotiques pour vaches taries aurait un effet bénéfique sur l'élimination des pathogènes intramammaires durant le tarissement. Un total de 425 quartiers positifs provenant de 270 vaches laitières de race Holstein-Friesian ont été utilisés dans l'essai. Des échantillons de lait ont été recueillis aseptiquement deux semaines avant la date prévue du tarissement, au moment du tarissement et une fois dans les huit premiers jours en lactation. Les quartiers infectés ont été alloués aléatoirement soit au traitement conjoint avec le scellant et l'antibiotique pour vaches taries ou soit au traitement avec l'antibiotique seul. Un quartier était déclaré guéri si les pathogènes isolés pendant le tarissement n'étaient plus présents postpartum. Le taux global de guérison bactériologique ne différait pas entre les deux traitements, c'est à dire le traitement conjoint scellant-antibiotique et le traitement antibiotique seul. De même, il n'y avait pas de différence entre le taux de guérison pour les infections dues à des pathogènes majeurs ou mineurs.

Introduction

Dry cow management continues to be an active area of research and has been reviewed extensively.[7] The current North American practice, recommended by the National Mastitis Council (NMC), for elimination of existing infections and prevention of new intramammary infections (IMI) during the dry period, is blanket dry-cow therapy. In other words, it is recommended to treat all quarters of all cows with an approved intramammary dry-cow antibiotic (DCT).[10,13] Blanket DCT has been successful in decreasing the incidence of new IMI during the dry period, particularly from gram-positive organisms, and also eliminates many existing IMI present at the end of lactation.[15,16] While dry-cow therapy is effective, it has limitations. Therapeutic levels of antibiotics are only present in the mammary gland for a limited period of time, and commercially available DCT in North America is targeted specifically against gram-positive bacteria.[4] As a result, quarters are left unprotected and susceptible to all types of new IMI in the latter part of the dry period, particularly to gram-negative infections.

Cure rates associated with DCT have been studied extensively and vary greatly.[7] Dry cow antibiotic cure rates have been reported to be as high as 94-98% for

Corynebacterium bovis[1,12] or as low as 20% for resistant *Staphylococcus aureus* infections.[10] There are large differences in cure rates when type or strain of pathogen,[17] or parity[5] are considered. Differences may also be attributed to herd-level factors, cow-level factors, management techniques, antibiotic selection, insertion techniques and research trial protocols.[3,8]

Availability of internal teat sealers (ITS) has created a new area of research and has been the topic of multiple clinical trials worldwide over recent years.[2,6,11,12,14,19] Internal teat sealers function as inert physical barriers in the teat cistern, with the goal of preventing the penetration of bacteria from the environment into the udder. As a non-antibiotic device designed to seal and protect the teat canal, ITS offer a unique opportunity to dairy producers to modify their dry cow management. ITS can be used alone in non-infected cows as a means to prevent new IMI and decrease the use of DCT; alternatively, they can be used in conjunction with DCT to provide protection beyond the scope achieved with DCT alone.

Internal teat sealers have no antibacterial properties. Therefore, ITS would not be expected to have any additional effect on cures of existing pathogens during the dry period. One study, however, found that ITS used alone had a spontaneous elimination rate of 63 and 59% on major and minor pathogens, respectively.[12] It is possible that the use of ITS in conjunction with DCT may have some additional benefit beyond the scope of prevention of new IMI. Many cows (and quarters) are dried off abruptly and leak milk for multiple days during the early dry period. This leakage may be caused from increased pressure in the unmilked mammary gland.[8] Clinical mastitis developed four times as often in cows that leaked milk after they were dried off when compared with cows that did not leak.[15] One possible explanation of this finding is that leaking can cause the teat canal to be patent and allow entry of bacteria. Also, DCT may have leaked from the gland and have been less effective. The addition of ITS to these quarters possibly prevents or reduces the amount of milk leaking out of the mammary gland, reducing flushing out the DCT. Another hypothesis is that a second intramammary infusion would induce a stronger local inflammatory response (higher numbers of leukocytes) in the mammary gland, which would secondarily assist the DCT in killing existing organisms.

No differences between cure rates of quarters treated with DCT and those treated with both DCT and ITS were found in previous studies.[6,11,19] All studies reported high cures with the DCT alone (80.6-88.2%), and DCT used in conjunction with ITS (83.0-91.3%). However, there were many management differences between the previous studies examining cure rate and the current study. In New Zealand, three large herds with seasonal calving were used to assess cure rates, where the distribution of dry-period pathogens was very different than the current study.[19] While the distribution of dry-period pathogens are very similar between the current study and the two USA trials, the management practices and herd sizes between the studies were vastly different.[6,11] Therefore, the main objective of this study was to assess whether using ITS in conjunction with DCT would have any additional benefit on the percentage of quarters cured during the dry period when compared with DCT alone.

Materials and Methods

Herd and Animal Selection

Sixteen herds in close proximity to the participating veterinary schools in Canada (PEI, Quebec, and Ontario) and the United States (Kansas) were selected. A total of 270 Holstein-Friesian cows provided data from 425 infected quarters (defined below). All milking cows in selected herds were eligible to participate if they had a positive culture result both two weeks prior to dry-off, and again on the day of dry-off. Study cows had to have at least three functional quarters, be confirmed pregnant and be in good physical condition.

Treatment Allocation and Sample Collection Schedule

Treatment allocation, sampling schedule and bacteriological culture procedures have been previously described.[14] In brief, milk samples were taken aseptically from all quarters of all cows at three points in time: two weeks prior to dry-off, at dry-off and after calving (1-8 DIM). A California Mastitis Test (CMT) was performed on the day of dry-off. CMT scores were assigned immediately on a scale of 0 to 3. Cows were defined as infected if a mammary pathogen was isolated from one or more quarters from the milk samples collected two weeks prior to dry-off. Quarters within these infected cows were sequentially assigned to one of two treatments in a split-udder design. Two ipsilateral quarters were assigned to receive an intramammary infusion of benzathine cloxacillin DCT,[a] and the remaining two ipsilateral quarters received the same DCT and were also infused with ITS.[b] For quarters that received both DCT and ITS, the DCT was administered first. Teats were disinfected using a commercial teat dip and then the cows were moved to each farm's dry cow area.

Definitions

Intramammary Infection (IMI): Isolation of any major mastitis-causing organism (i.e. *Staphylococcus aureus, Streptococcus agalactiae*, other *Streptococcal* spp, coliforms, *Arcanobacterium pyogenes, Prototheca* spp, *Proteus* spp, *Citrobacter* spp, or yeast) or more than

10 colony forming units (cfu) of a minor mastitis-causing organism (i.e. *Corynebacterium bovis* or coagulase-negative staphylococci (CNS)), resulted in a quarter being defined as having an IMI. As noted above, cows were classified as infected (for the purpose of treatment allocation) if one or more quarters had IMI at the sampling done two weeks prior to dry-off. For this study, only quarters which had IMI at the time of drying off were considered in the analysis.

Major pathogen cure: A quarter was defined as cured if all of the major bacteriological pathogens that were isolated at the dry-off sample were not present at the post-calving sample.

Minor pathogen cure: A quarter was defined as cured by isolation of less than 10 cfu of minor pathogen(s) in a quarter that had previously isolated more than 10 cfu.

Overall cure: A quarter was defined as cured if all of the pathogens isolated at the dry-off sample were not present at the post-calving sample. A quarter was still considered to be cured if a new (different) pathogen was isolated post-calving.

Contaminated sample: A milk sample was considered contaminated if three or more pathogens were isolated.

Statistical Analysis

The primary experimental unit was the individual quarter, and only infected quarters (i.e. IMI present at dry-off) were considered. A generalized linear mixed model (-gllamm- macro in Stata 8.2)[18] was used to analyze risk factors for the probability of a quarter cure during the dry period.[9] Three separate analyses were performed: cure of all pathogens, cure of major pathogens and cure of minor pathogens. Factors controlled for and considered were quarter, parity, dry period length, dry period season, dry-off treatment, CMT score at dry-off, SCC at dry-off (log transformed, lnSCC/1000), housing type, herd size and all biologically plausible first-order interactions. All analyses controlled for clustering of quarters within cow and cows within herd. Unconditional associations were performed to select predictors for each full model. All predictors with a $P < 0.25$ for an unconditional association with the outcome were retained for evaluation in the multivariable model. A backwards step-wise elimination process was utilized for model reduction, using a significance level of $P < 0.05$. The potential confounding effect of factors removed was evaluated by examining the change in the estimate of the treatment effect upon their removal.

Results

Descriptive Statistics

A total of 210 infected quarters were treated with DCT alone, and 215 were treated with both DCT and ITS. After all exclusion criteria were considered (Table 1), data from 388 quarters (245 cows) were available for the analysis.

The infected quarters at dry-off were evenly distributed: 96, 101, 98 and 93 from left front, left hind, right front and right hind, respectively. There were three missing scores for the CMT, otherwise 43.3, 28.4, 16.6 and 11.6% of the quarters scored 0, 1, 2 and 3, respectively. SCC values were missing from 60 of the quarters. Of the remaining 362, mean lnSCC was 5.3 (SD 1.7) ranging from 0-9.21.

Mean parity for the study cows after calving was 3.3 (median 3, range 2-9). Average dry period length was 60 days (standard deviation 17.4) and the dry periods studied were evenly distributed across seasons (winter 22.2%, spring 25.7%, summer 26.1%, fall 26.1%). Average herd size was 123 (median 100, range 40-380). Eight of the study herds used free-stall housing, and the remaining eight herds used tie-stall housing. Pathogens isolated at dry-off, along with their cure rates, are summarized in Table 2. Total number of infections is higher than the number of quarters in each treatment group because a quarter could have multiple pathogens. Total pathogen cure rates across treatments were quite high (88.7 and 85.3%) from the DCT/ITS and the DCT, respectively. No differences were found between treatment groups. Average pathogen cure rates, across treatments, were slightly higher for minor versus major pathogens. Highest pathogen cures were seen for *S. agalactiae* and yeast (100%), although there were few IMI with these organisms at dry-off. Lowest cures were found for *S. aureus* (76.7 and 75.9% in the DCT/ITS and the DCT treatment groups, respectively).

Quarter Cure of Major Pathogens

Only quarters containing a major IMI at dry-off were considered in this analysis. Quarters containing a mixed major IMI were only considered cured if both pathogens isolated at dry-off were not isolated at the post-calving sample. Unconditional associations between the follow-

Table 1. Description of exclusion criteria and number of quarters affected with treatment groups (Dry Cow Therapy and Internal Teat Sealer (DCT/ITS or Dry Cow Therapy (DCT)).

	DCT/ITS (n = 215 qtrs)	DCT (n = 210 qtrs)
No post-calving sample	13	9
Additional dry-off antibiotics	5	3
Additional post-calving antibiotics	4	3
Total remaining quarters	193	195

ing predictors and cure of a major pathogen gave values that allowed them to be utilized in model building: quarter (P = 0.06), dry period length (P = 0.04), dry period season (P = 0.03), CMT (P < 0.01), lnSCC (P = 0.09), herd size (P = 0.01), housing (P = 0.19) and parity (P = 0.24). Treatment was again forced into the model. The data from 151 quarters (112 cows) were utilized in the final model as only quarters containing major pathogens were considered. The full multivariable regression model is shown in Table 3. No treatment effect was found. Quarters treated with DCT and ITS had an 83.8% cure rate, whereas quarters treated with DCT had an 87.9% cure rate. There was no evidence of a cow or herd effect on cure rate, as variance estimates were non-significant.

Quarter Cure of Minor Pathogens

A total of 256 quarters from 183 cows were identified as having IMI caused by minor pathogens at dry-off and were considered in the analysis. Unconditional associations between the following predictors and cure of a minor pathogen gave values that allowed them to be utilized in model building: quarter (P = 0.12), dry period length (P = 0.07) and lnSCC (P = 0.11). Treatment was forced into the model as well. The full multivariable regression model is shown in Table 4. No treatment effect was found. Quarters treated with DCT and ITS had a 92.2% cure rate compared with 87.5% cure rate in the DCT group. No cow or herd effect on cure rate was evident as the variance estimates were non-significant.

Quarter Cure of All Pathogens

Unconditional associations between the following predictors and cure of all pathogens during the dry period gave values that allowed them to be utilized in model building: dry period length (P = 0.19) and CMT (P = 0.25). Treatment was forced into the model as this was the predictor of interest. The data from 388 quarters (245 cows) was utilized in the final model. The full multivariable regression model is shown in Table 5. No treatment effect was found. Quarters treated with both DCT and ITS had a 79.6% cure rate compared to 78.9% of quarters treated with DCT alone. Overall quarter cure rates are lower than quarter cures for either major or minor pathogens. Any quarter could contain multiple pathogens and all had to be eliminated to be considered in this category. There was no evidence of either a herd or cow effect on the overall cure rates (both variance estimates were non-significant).

Discussion

No additional benefit in percentage of quarters cured was found when using ITS in addition to DCT

Table 2. Distribution of pathogens between treatment groups at dry-off and proportion of pathogen cures from 388 quarters.

	DCT / ITS		DCT	
	Dry	Cure (%)[1]	Dry	Cure (%)[1]
Major pathogens				
Staphylococcus aureus	34	26 (76.5)	29	22 (75.9)
Streptococcus agalactiae	0	-	2	2 (100.0)
Other streptococci	27	25 (92.6)	27	24 (88.9)
Gram negatives	17	14 (82.4)	19	18 (94.7)
Yeast	1	1 (100.0)	2	2 (100.0)
Mixed major[2]	2	1 (50.0)	6	2 (33.0)
Total major	79	66 (83.5)	79	68 (86.1)
Mixed major and minor	13	11 (84.6)	6	4 (66.7)
Minor pathogens				
Coagulase-negative staphylococci[3]	124	113 (91.1)	127	108 (85.0)
Corynebacterium bovis[3]	9	9 (100.0)	5	4 (80.0)
Mixed minor	4	4 (100.0)	5	4 (80.0)
Total minor	133	122 (91.7)	132	112 (84.8)
Overall total pathogens[4]	212	188 (88.7)	211	180 (85.3)

[1] Cure percentages based on a single milk sample, therefore overestimated
[2] Quarter containing two major pathogens
[3] > 10 cfu
[4] Pathogen cures calculated differently from quarter cure rates (in text)

Table 3. Logistic regression model analysis of odds of curing an intramammary infection during the dry period caused by major pathogens (n = 151 quarters).

Variables	Coefficient	Standard Error	Odds Ratio	95% Confidence Interval of Odds Ratios	*P*-value
Fixed effects					
Constant	1.99	0.47			
Treatment					
Dry cow antibiotic	ref.				
Internal teat sealer/dry cow Antibiotic	-0.35	0.50	0.71	0.27, 1.86	0.48
	Variance	Standard Error[a]			
Random effects					
Herd	0.71	0.63			
Cow	<0.01	<0.01			

[a] Standard error of estimate of variance component

Table 4. Logistic regression model analysis of odds of curing an intramammary infection during the dry period caused by minor pathogens (n = 256 quarters).

Variables	Coefficient	Standard Error	Odds Ratio	95% Confidence Interval of Odds Ratios	*P*-value
Fixed effects					
Constant	1.95	0.44			
Treatment					
Dry cow antibiotic	ref.				
Teat sealer/dry cow antibiotic	0.52	0.42	1.68	0.74, 3.83	0.22
	Variance	Standard Error[a]			
Random effects					
Herd	<0.01	<0.01			
Cow	0.21	0.94			

[a] Standard error of estimate of variance component

when compared with DCT used alone. Previous ITS studies also found no additional cure benefit to using both ITS and DCT.[6,11,19] The cure rates found in this study are consistent with previous literature[6,11,19] and were high. Both major and minor pathogens had similar quarter cure rates. The overall quarter cure rate was lower than both the major and minor quarter cure. It is less likely to cure multiple pathogens in a quarter than single pathogens.

Parity, dry period length, dry period season, quarter, housing, herd size or SCC at dry-off were not found to have any impact on cure rates, no matter whether all, major or minor pathogens were considered. Only one DCT was evaluated, so all estimations of cure are only relevant to this product.[a]

Achieving the objectives of this study relied upon determination of quarter IMI status at the time of calving. Quarter cure was defined by using a single milk bacteriological culture to isolate a pathogen from a quarter post-calving that was previously isolated at dry-off. Using one sample postpartum will overestimate cure rates because of the high false-negative rate (i.e. quar-

Table 5. Logistic regression model analysis of odds of curing an intramammary infection during the dry period caused by all pathogens (n = 388 quarters).

Variables	Coefficient	Standard Error	Odds Ratio	95% Confidence Interval of Odds Ratios	*P*-value
Fixed effects					
Constant	1.32	.25			
Treatment					
Dry cow antibiotic	ref.				
Internal teat sealer/dry cow Antibiotic	0.04	0.26	1.04	0.62, 1.75	0.87
	Variance	Standard Error[a]			
Random effects					
Herd	<0.01	<0.01			
Cow	0.85	0.63			

[a] Standard error of estimate of variance component

ters which were still infected, but from which the organism was not isolated). This is particularly true when assessing *S. aureus*. Previous research has concluded that multiple cultures are required to specify a cure of this pathogen.[8] Therefore, the current study has overestimated the cure of *S. aureus*, although this exaggeration would not be expected to be different across treatment groups. While multiple milk samples used in serial will increase the chance of detecting a pathogen (increase sensitivity) there will be an associated decrease in specificity (more false positives) due to the isolation of organisms from infections which developed after calving. Regardless of the number of samples taken errors will occur. Hence, some misclassification bias will be present. However, this bias would be expected to be the same in both of the treatment groups, and therefore would be non-differential misclassification.[9] When dichotomous (yes/no) outcomes are measured, non-differential misclassifications always bias the measure of association, in this case odds ratio, towards the null.[9] Therefore, the estimates of treatment effects from our data would be conservative, but our estimates of quarter cure would be exaggerated. However, it is unlikely that the bias of treatment effect toward the null would have accounted for the complete lack of evidence of any treatment effect if even a modest effect had been present. Some previous ITS studies have also used one sample post-calving, and emphasized that care must be taken when interpreting results for cure.[11,12]

Conclusions

ITS used in conjunction with DCT did not have a beneficial effect on quarter cure when compared with using DCT alone. It should be emphasized that the primary use of ITS is for the prevention of new IMI during the dry period. The device has no antibacterial properties, and therefore proper aseptic technique must be used when infusing this product into the mammary gland.

Endnotes

[a] DryClox®, Ayerst Veterinary Laboratories, Guelph, Canada.

[b] OrbeSeal*, Pfizer Animal Health, Montreal, Canada.

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Abstract

Efficacy of Diclazuril (Vecoxan™) Against Naturally Acquired Eimeria Infections in Suckling Calves and Economic Benefits of Treatment

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Diclazuril has been developed and is currently available as an oral suspension (Vecoxan®) for prevention and treatment of coccidiosis in lambs. Claves are also susceptible to protozoal infections, and coccidiosis due to *E. bovis* and/or *E. zuernii* is often diagnosed as one of the causes of diarrhea and poor performances in claves between one and 6 months of age. Also subclinical coccidiosis is recognized to have a negative impact on growth performances of ruminants.

The present field efficacy studies were designed to confirm the efficacy of diclazuril in naturally infected calves under field conditions. The efficacy of a single dose of 1 mg diclazuril per kg body weight, administered as an oral suspension, against natural infections with *Eimeria* spp. was investigated in suckling Charolais beef calves. On one of the trial sites, 64 and 30 calves were divided into two groups: an untreated control group and a diclazuril treated group. The treatment was given metaphylactically, when the calves were on average 1.5 months of age, before outbreaks of clinical coccidiosis were expected. For three weeks after the treatment, fecal scores were noted daily, and faecal oocyst counts and oocyst differentiation was determined every second day to evaluate the reduction in faecal oocyst exceretion, particularly for the pathogenic species *E. bovis* and *E. zuernii*. The results clearly demonstrate that natural infections with *E. bovis* and *E. zuernii* in calves can be controlled with a single oral diclazuri treatment at 1 mg per kg BW. The reduction in oocyst shedding over the 3 weeks post treatment observation period was more than 99% for both *E. bovis* and *E. zuernii*.

Even though the majority of the control calves did not develop clinical coccidiosis on the trail sites, the diclazuril treated calves had a better mean weight gain of 6kg and 2.1kg over calves with clinical and subclinical coccidiosis respectively over the post treatment period. The major weight loss at an individual level is in the clinically affected calves but at herd level the sub-clinically affected calves account for 64% of the loss, compared to overall weight loss of 36% in the clinically diseased calves.