PROFESSIONAL SERVICES
Boehringer Ingelheim Vetmedica, Inc.

TECHNICAL BULLETIN

Randomized Non-Inferiority Clinical Trial Evaluating Three Commercial Dry Cow Mastitis Preparations.

Based on Publications:

National Mastitis Council. *52nd Annual Meeting Proceedings*. January 27-29, 2013. San Diego, California.

A. G. Arruda, S. Godden, P. Rapnicki, P. Gorden, L. Timms, S. S. Aly, T. W. Lehenbauer, J. Champagne. Randomized noninferiority clinical trial evaluating 3 commercial dry cow mastitis preparations: I. Quarter-level outcomes. *J. Dairy Sci*. 2013 Jul; 96(7): 4419-4435.

Overview

A large clinical trial was conducted to compare the treatment efficacy of three dry cow formulations: ToMORROW® (300mg cephapirin benzathine, Boehringer Ingelheim Vetmedica, Inc.(BIVI)), Spectramast DC (500mg ceftiofur HCL, Zoetis Animal Health) and Quartermaster (1 x 10^6 units penicillin G and 1 g dihydrostreptomycin, Zoetis Animal Health). The study was conducted over multiple states WI (2), MN(1), IA (1) and CA (2) with 363 cows (1,452 quarters) randomly allocated per treatment. All quarters were also infused with Orbeseal.

There was no difference among the preparations in the following quarter-level outcomes.

- The prevalence of intramammary infections (IMI) post calving
- Ability to cure pre-existing IMI during the dry period
- Ability to prevent new IMI during the dry period
- Risk for a clinical mastitis event between calving and 100 days in milk (DIM)

There was also no difference in the following cow-level outcomes to 100 DIM.

- Milk production (305ME)
- Linear score
- Risk for a clinical mastitis event
- Risk for leaving the herd
- Risk for getting pregnant

Introduction

Dry cow mastitis treatment is a well established management practice intended to cure existing IMI acquired during lactation and to prevent new IMI in the dry period. The prevalence of subclinical IMI at dry off can vary between 13 and 35% and the incidence of new IMI during the dry period can vary from 8 to 25%. (Godden et al. 2003). The majority (50 to 60%) of all new infections, caused by environmental pathogens, occur during the dry period (Bradley and Green 2000).

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Materials and Methods

The study was designed to detect a 10% difference in treatment effects at the quarter level. Inclusion criteria for cows in the study included four functional quarters, good general health, the herd be on regular DHIA testing, no clinical mastitis at dry off and no history of having been treated with antibiotics or anti-inflammatory drugs within 30 days prior to enrollment. All study enrollment and sampling activities were conducted by University technicians who visited the herd on dry off day each week.

Milk culture and pathogen identification techniques were in accordance with National Mastitis Council guidelines.

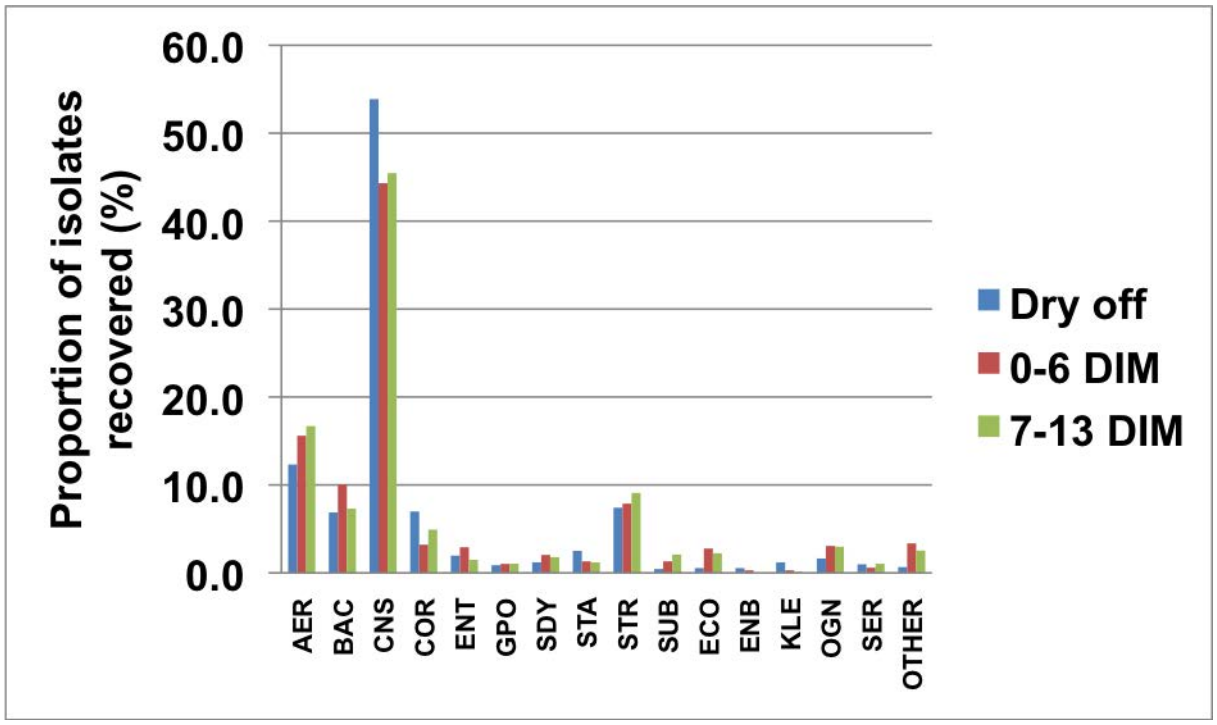
The definitions for defining Intramammary infection status were as follows:

- Presence of an IMI:
  - Most pathogens: ≥ 1 colony isolated in 10 µl of milk
  - CNS ≥ 2 colonies
  - *Bacillus* spp. ≥ 5 colonies
- Bacteriologic cure of an IMI:
  - Disappearance of 1 or 2 pathogens that were previously isolated at the dry off milk sample from both post calving samples
- New IMI:
  - Growth of 1 or 2 pathogens that had not been previously isolated in the dry off milk sample in either the 0-6 DIM or 7-13 DIM sample

Results

The IMI pathogens isolated during the study are displayed in Chart 1.

Chart 1.



(AER) *Aerobacter* spp., (BAC) *Bacillus* spp., CNS (Coagulase neg *staphylococcus*), COR (*Corynebacterium* spp.), ENT (*Enterococcus* spp.), GPO (Other gram positive), SDY (Other *Streptococcus* spp.), STA (*Staphylococcus aureus*), STR (*Streptococcus dysgalactiae*), SUB (*Streptococcus uberis*), ECO (*Escherichia coli*), ENB (*Enterobacter* spp.), KLE (*Klebsiella* spp.), OGN (Other gram negative), SER, (*Serratia* spp.)

At dry off, 94.4 % of the IMI were Gram positive and 4.9 % Gram negative. After calving (0-6 DIM), 89.7 % of the IMI were Gram positive and 7% Gram negative. The culture results were consistent with the pathogen profiles from dry off and freshening cows in the modern dairy industry; the majority of isolates were environmental Gram positives, with CNS spp. predominating. Contagious pathogens, which traditionally have been the major target for dry cow therapy, were either totally absent (*Streptococcus agalactiae*) or were a very small percentage of isolated IMI (*Staphylococcus aureus*, 2.5% and 1.3% at dry off and 0-6 DIM, respectively).

Statistical analysis of the results was performed with SAS 9.2. A logistic regression model was used for risk of IMI prevalence and cure. A mixed linear model was used for milk production and linear score to 100 DIM. Survival analysis was used for risk of clinical mastitis, risk of leaving herd and the risk of becoming pregnant by 100 DIM.

A comparison of prevalence of IMI at dry off, cure and new IMI among the three dry cow therapies are shown in Table 1.

Table 1.

	QM	SP	TM	P*
IMI present at Dry off	18.8%	18.2%	20.7%	0.58
IMI present at 0-6 DIM	15.4%	13.2%	15.3%	0.3
IMI present at 7-13 DIM	15.4%	14.9%	13.7%	0.41
Cure	89.8%	88.6%	90.0%	0.72
New IMI at 0 -6 DIM	14.9%	12.3%	14.2%	0.27
New IMI at 7 -16 DIM	17.9%	17.2%	16%	0.6
Risk of Clinical Mastitis in Qtr to 100 DIM	5.3	3.8	4.1	0.27

*Significance declared at P < 0.05

Cow level variables analyzed are shown in Table 2.

Table 2.

	QM	SP	TM	P*
Risk of mastitis to 100 DIM	14.8	12.7	15	0.8
Milk production (kg/day)	42.9	42.1	42.8	0.14
Linear Score (L2)	1.9	2.0	1.7	0.12
Risk of leaving herd to 100 DIM	7.5%	9.2%	10.3%	0.55
Risk of pregnancy by 100 DIM	31.5%	26.1%	26.9%	0.26

*Significance declared at P < 0.05

Discussion

This study, which was designed as a non-inferiority study, demonstrated no significant difference among the three dry cow intramammary preparations.

The majority of pathogens isolated in this study were CNS *spp*. and the results reflect the preponderance of this organism in all sampling stages. Although the numbers are small, the biggest disparity in cure rates by pathogen was for *Staphylococcus aureus*. The number of quarters at risk of a cure and the cure rate (CR) are as follows for each treatment; QM (n = 5) , CR = 80%; SP (n = 7), CR = 42.7%; TM (n = 9), CR = 88.9%. TOMORROW, a first generation cephalosporin has a more robust Gram positive spectrum than a third generation cephalosporin. TOMORROW's cure rate for *S.aureus* at 88.9% approached statistical significance (one sided p-value <0.08.) when compared to Spectramast's cure rate at 42.7%

The factors examined in this study are the most economically important to consider in selecting a dry cow intramammary preparation. However, given that all these preparations yielded similar results, other factors would need to be considered in herds that have a similar pathogen profile.

These factors include judicious use of antimicrobials, milk withhold after calving, meat withhold times and the cost of the dry cow therapy.

From the point of view of judicious use of antibiotics, the authors suggest that the veterinary community should consider the use of first generation cephalosporins over the use of third generation cephaloporins.

The cost of the different dry cow preparations with regard to milk withhold depends on available uses for milk from treated animals. This non-saleable milk can be very valuable if fed to calves, so the cost may in fact be zero or minimal depending on the market milk price and the cost of milk replacer powder.

The milk withhold (hours non-saleable) difference between two products should be calculated as the time difference to when milk is marketed. Most dairies still collect colostrum from zero hold milk dry cow therapies and it may be 12 to 24 hours before these cows actually have milk marketed.

A dairy manager may elect to sell a cow after treatment with a dry cow preparation due to abortion or other problems. These cows need to clear the meat residue withhold times before sale. However, because these cows represent a very small percentage of all the cows dry-treated, the cost is minimal. The TOMORROW calculator was introduced by BIVI in 2012 to help dairy managers consider important factors when making decisions regarding the choice of dry cow treatments. Using typical figures of cows sold out of the dry pen in the TOMORROW calculator, the cost difference calculated for the different meat withhold days of dry cow tubes varies from less than $1 to $2 per treated cow.

There is no difference in the effectiveness of the therapies. The cost difference between therapies is easily calculated. The financial analysis should include the cost of withholding the milk and the cost of meat withhold. The TOMORROW calculator takes all the above factors into account and helps determine which dry cow therapy is the most economical to use on a particular operation.

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