Research Review

PRODUCT REVIEW

Cephalonium (Cepravin® Dry Cow)

About the Reviewer

Hamish Newton

Hamish Newton graduated from Massey University with a BVSc in 1998 and started working in mixed practice at the Veterinary Centre – Oamaru. He then worked in mixed practice in the UK before starting a PhD at Bristol University examining factors that influence the cure of intramammary infections in the involuting mammary gland. Upon completing his PhD in 2007 he returned to the Veterinary Centre – Oamaru and became a partner in 2008. He now spends most of his working time dealing with dairy cows.

This review is intended as an educational resource for veterinary health professionals and dairy farmers. It is a concise summary of mastitis and its management, with a focus on the first-generation intramammary cephalosporin antibiotic cephalonium (Cepravin® Dry Cow). This review is funded by MSD Animal Health.

Background to Dairy Cow Mastitis

Intramammary infections that are acquired by dairy cows during the dry (non-lactating) period or that remain from the previous lactation are sources of clinical (symptomatic) and subclinical (non-symptomatic) mastitis during the new lactation.[1] Cows are at high risk of developing intramammary infections during the dry period and these infections often remain quiescent until parturition.[2] Although a variety of micro-organisms can cause intramammary infections, bacteria are the most frequent pathogens of this disease.[3]

There has been a marked changed in the prevalence and aetiology of mastitis in New Zealand dairy cows in the past half-century, with changes in prevalence likely due to changes in mastitis control strategies.[3-5] A notable feature of this epidemiological transition has been a decrease in the prevalence of contagious mastitis pathogens and an increase in the prevalence of environmental pathogens, in particular *Streptococcus uberis*.[3-5]

In 1948, the prevalence of mastitis was estimated to be 45%, with *Streptococcus agalactiae* being the primary causative organism in clinical and subclinical mastitis. By mid-1960s, however, *Staphylococcus aureus* was reported to be the most common cause. As of the middle to late 1990s, mastitis prevalence estimates of 10% in cows[5] and 8.1% in heifers[6] on Waikato farms had been reported, and *Strep. uberis* and coagulase-negative staphylococci had become the most important species causing mastitis in New Zealand.[3,5] More recently, the incidence of clinical mastitis has been estimated to be 14.8% in lactating cows in Northland dairy herds,[7] and the cumulative lactation incidence of clinical mastitis in New Zealand dairy cows was 11% in a genetics-based study.[8]

Mastitis due to *Escherichia coli* appears to be low in New Zealand relative to the Northern Hemisphere, which may be due to New Zealand dairy cows being pastured rather than housed.[3,9] Indeed, intramammary infection with coliform bacteria is a recognised problem in dairy cattle managed under confinement systems, but not in cows under pasture-grazing systems in New Zealand. The difference may be attributable to the high exposure of pasture-grazed animals to *Strep. uberis* and competitive inhibition by *Strep. uberis* of coliform bacteria.[9]

Economic Burden of Dairy Cow Mastitis

Clinical mastitis in dairy cows has a negative effect on animal health, longevity, and milk production.[3,10-16] Clinical mastitis that occurs soon after calving and before maximum milk-yield is particularly costly because milk-yield losses and the risk of culling or death are increased compared with infections that occur later in the lactation period.[15,16] Subclinical mastitis can also depress milk production and cows with subclinical mastitis have a higher risk of progressing to clinical mastitis than non-infected cows.[13,17]

Economic losses due to clinical mastitis have been estimated at €61 to €97 per cow per year in European studies published between 2008 and 2009.[18] These losses are comparable to those for lameness (€75 per cow per year) and reproduction (€88 per cow per year), indicating that mastitis is an expensive disease on dairy farms.[18]

Mastitis has also been demonstrated to be an economically important disease in New Zealand dairy herds.[19] An economic evaluation reported by the National Mastitis Advisory Committee conservatively estimated that for a representative New Zealand farm in 2006 the average cost per cow of clinical mastitis was $36.50, or $11,500 per average herd, equivalent to $180 million for the New Zealand dairy industry.[19] Economic losses were associated with reduced milk production due to both clinical and subclinical mastitis, discarded milk during the withholding periods, treatment-associated costs, reduced milk price due to a high somatic cell count (SCC) and the culling of persistent mastitis-infected cows.[19]

In both the European and New Zealand economic analyses, the financial burden of mastitis was primarily due to lower milk production per cow.[18,19] Production losses can therefore be avoided by reducing the number of clinical mastitis events in a dairy herd.

Economics of Management of Dairy Cow Mastitis

The choice of control strategies to help to reduce mastitis events should be based on objective economic calculations. In a cost-effectiveness analysis of mastitis control strategies implemented for a default dairy farm in the Netherlands, six of 18 control measures produced a positive net financial benefit, all of which required relatively low additional expenditure (**Table 1**).[18] Dry-cow therapy was associated with the greatest financial benefit, supporting the justification for dry-cow therapy being that treatment costs will be outweighed by the production gains achieved via elimination of infection and prevention of new infection.[20] The other five financially-beneficial measures identified in the cost-effectiveness analysis were washing dirty udders during preparation of the udder, use of milkers' gloves during milking, back-flushing clusters after milking a cow with clinical mastitis, use of a treatment protocol, and keeping cows standing after milking,[18] some of which are not directly applicable to a New Zealand dairy herd.

Management measure	Additional expenditure	Reduced losses	Net benefit
Milk cows with clinical mastitis last	37	16	–21
Milk cows with subclinical mastitis last	104	20	–84
Use of separate cloths during preparation of udder	26	9	–17
Wash dirty udders during preparation of udder	3	9	6
Pre-stripping	34	9	–25
Use of milkers' gloves during milking	1	9	8
Teat disinfection post-milking	31	31	–0
Back-flushing clusters after milking a cow with clinical mastitis	1	11	10
Back-flushing clusters after milking a cow with subclinical mastitis	123	15	–108
Replace teat-cup liners in time	13	11	–2
Use of a treatment protocol	7	15	8
Application of blanket dry-cow therapy	9	36	27
Keep cows standing after milking	2	12	10
Feed additional dry-cow minerals	13	13	0
Prevent overcrowding	23	13	–10
Clean cubicles	54	15	–39
Clean yards	51	8	–43
Optimise feed ration	24	13	–11

Table 1. Comparison of the net financial benefit (€/cow/year) of implementing different mastitis prevention measures calculated for a generic dairy farm of 65 cows in the Netherlands with an average 305-day milk production of 8,500 kg/year, an average bulk tank SCC of 200,000 cells/ml, an incidence of clinical mastitis of 30% per year (65% environmental and 35% contagious), and a milking parlour with 12 stands.[18]

KEY STUDY

Economic aspects of mastitis: new developments[18]

Authors: Hogeveen H, et al

Methodology: These Dutch researchers estimated the cost effectiveness of various measures to prevent clinical mastitis by repeating, with an improved design, a previously published analysis[21] that determined the costs and efficacies of 18 different management measures to control mastitis. In the original analysis, the efficacies were determined by combining literature data and expert opinion using Monte Carlo expert evaluation analysis and calculations were based on a default farm of 65 dairy cows with average mastitis conditions (bulk tank SCC of 200,000 cells/ml and an incidence of clinical mastitis of 30%).[21]

Results: In this re-analysis, six out of the 18 preventive measures were predicted to have a positive net financial benefit (**Table 1**). In order of decreasing benefit they were: blanket use of dry-cow therapy > keeping cows standing after milking > back-flushing of the milk cluster after milking a cow with clinical mastitis > application of a treatment protocol > washing dirty udders > use of milkers' gloves. All six measures required relatively low additional expenditure. In contrast, the preventive measures with the least financial benefit, back-flushing the milk cluster after milking cows with subclinical mastitis, and milking cows with subclinical mastitis last, required the highest additional expenditures.

Conclusions: The researchers concluded that not all measures that reduce losses due to mastitis are cost effective and that for good decisions to be made, it is necessary to provide dairy farmers with objective information on the additional expenditure and reduced losses associated with the different alternative decisions.

Expert Comment
Cost-effective management measures for the control of mastitis may not always be implemented due to allocation of limited resources, risk involved with the management decision, and the valuation of cost by individual farmers. Blanket dry-cow therapy in this study was one of only six factors that showed a net benefit. Although this study was based on a Dutch farm assuming 65 cows, there are relevant messages for farmers in New Zealand. The management measures associated with the biggest reduced losses were associated with the biggest additional expenditure in this study, such as milking sub-clinically infected and clinically-infected cows last. These practices in a New Zealand context are not likely to be associated with a great deal of additional expenditure (increase in labour) as it is often normal practice to run two or more herds routinely. This study showed a benefit by keeping cows standing after milking, which, although not directly relevant to most New Zealand systems, could highlight the importance of well-maintained exit tracks to reduce the environmental exposure of the teats prior to the teat end closing after milking.

Dry-Cow Therapy

Antibiotic dry-cow therapy and the treatment of intramammary infection during drying off has been the foundation of mastitis management,[2] and is a key strategy in the Seasonal Approach to Managing Mastitis (SAMM) plan since it was first introduced in New Zealand in the early 1990s and in the updated SmartSAMM programme for control of mastitis control in the 2000s.[22]

The role of antibiotic dry-cow therapy is to:

- cure existing intramammary infections at drying off
- prevent new intramammary infections during the dry period.[23]

Cure rates for dry-cow therapy depend on the pathogen, duration of infection, dose rate and type of antibiotic, and the antibiotic vehicle use. Specific animal factors, including age, SCC at time of treatment, and number of times *Staph. aureus* was isolated before drying-off, are also important influencing factors.[24]

In addition to antibiotic therapy, the use of internal teat sealants as a prophylactic intervention has become an increasingly common part of dry-cow management.

The role of internal teat sealants is to:

- protect udders during the dry period and at calving
- extend the protection provided by dry-cow therapy.[23]

The prophylactic efficacy of teat sealant, used alone and in combination with dry-cow antibiotic therapy, has been demonstrated.[25,26]

Bacterial resistance

The development of bacterial resistance to antibiotics is a concern in any situation involving the extensive use of antibiotic therapy. Currently, there is limited evidence of antimicrobial resistance associated with antibiotic dry-cow therapy in New Zealand and the risk of mastitis pathogens developing antibiotic resistance appears to be relatively low.[27] Nevertheless, the Veterinary Council of New Zealand's Code of Professional Conduct defines the requirements for prescription of antibiotics in The Dry Cow Therapy Standard to support and promote the prudent use of antibiotics in animals and help minimise the potential for antibiotic resistance to develop. The use of multiple mastitis control measures is recommended to limit the quantity of antibiotics used and hence selection pressure for antibiotic resistance.[28]

Cephalonium

Cephalonium in a long-acting base (Cepravin® Dry Cow) is a restricted veterinary medicine that is indicated for dry-cow therapy, in conjunction with proper management of the cow during drying-off and over the dry period, to:

- reduce new infections at drying off and in the dry period;
- treat subclinical mastitis that may be present at drying off; and
- help to reduce SCC and mastitis in the subsequent lactation.[29]

Spectrum of activity

Cephalonium is a first-generation cephalosporin antibiotic that has a broad-spectrum antibacterial activity, with an initial high concentration being effective in treating existing infections, including those caused by *S. aureus*, coagulase-negative staphylococci, *S. uberis*, *S. agalactiae*, *Streptococcus dysgalactiae*, Corynebacterium and *E. coli*. Additionally, effective concentrations of

cephalonium protect against Staphylococcal and Streptococcal infections for up to 10 weeks and *E. coli* infections for up to 4 weeks. Cephalonium has also been shown to be associated with earlier teat closure.[29]

Therapeutic studies

Cephalonium produced cure rates of between 83% and 100% in New Zealand dairy herds in four prospective therapeutic studies published between 1995 and 2010, indicating the effectiveness of cephalonium as a dry-cow therapy in terms of cure of existing intramammary infections and prevention of new intramammary infections.[24,25,30,31]

Dosage and administration

Dry-cow therapy with cephalonium must be initiated ≥49 days before calving. Each cow should be treated immediately following its final milking for the season and administration must not be delayed. The dosage is one syringe of cephalonium 250mg per quarter.[29]

Care must be taken during the administration process not to introduce infection into the udder. First, the teat should be cleaned thoroughly with a fresh teat wipe and allowed to dry. After insertion of the nozzle (either partial or full insertion), the full contents of the syringe should be infused into the teat canal. Lastly, the teat should be sprayed carefully with an approved teat spray.[29]

Dry-cow therapy with cephalonium should be used once at drying off only and is not indicated for use in lactating dairy cows.[29]

KEY STUDY

The use of a cephalonium containing dry cow therapy and an internal teat sealant, both alone and in combination[26]

Authors: Bradley AJ, et al

Methodology: This randomised, controlled, therapeutic trial assessed the efficacy of different dry-cow therapy regimens by stratifying cows by likely infection status at drying off in herds with low SCC (bulk tank SCC <250,000 cells/mL) in southwest England. A total of 890 (457 high-SCC infected and 433 low-SCC uninfected) cows were enrolled from 6 farms. Data from a total of 810 and 839 cows were incorporated into the analyses pertaining to dry period intramammary infection and clinical mastitis, respectively. Quarters in high-SCC—infected cows were randomly assigned to receive cephalonium 250mg (Cepravin® Dry Cow) alone or in combination with an internal teat sealant (65% bismuth subnitrate in a mineral oil base, Teatseal®). Quarters in low-SCC—uninfected cows were randomly allocated to receive teat sealant alone or in combination with antibiotic dry-cow therapy.

Results: Cure rates for existing intramammary infection with major pathogens were consistently >90% in quarters receiving cephalonium (**Table 2**). Compared with antibiotic alone, combination therapy in high-SCC—infected cows increased their likelihood of being pathogen-free after calving (odds ratio [OR], 1.40; 95% credibility interval [CI]: 1.03-1.90) and reduced their likelihood of developing clinical mastitis in the first 100 days of the subsequent lactation (OR 0.68; 95% CI: 0.48-0.98). In contrast, combination therapy in the low-SCC—uninfected cows was not significantly different from teat sealant alone for the same outcomes.

Conclusion: The investigators concluded that significant benefits are associated with cephalonium and teat sealant used in combination in high-SCC—infected cows at drying off. The decision to treat low-SCC—uninfected cows with combination therapy is less straightforward, requiring consideration of the prevalence of different pathogens within the herd as well as the need to manage the current level of bulk tank SCC.

Expert Comment

Cows at drying off were categorised as infected or uninfected based on the SCC and mastitis history of each cow. All quarters in infected cows received cephalonium and half also received an internal teat sealant. All quarters in cows deemed uninfected received teat sealant and half also got cephalonium. In the infected cows, the quarters that received both cephalonium and internal teat sealant were more likely to be free of a major pathogen post calving and less likely to experience clinical mastitis in the first 100 days of lactation compared to quarters that received cephalonium alone. These results measured at the quarter level and the approach to classify a cow as infected, or not, are broadly similar to the 'matrix approach' to selecting dry-cow therapy described on page 5 of Technote 14 (SmartSAMM). The above study though does not attempt to classify farms as at risk of contagious or at risk of environmental mastitis. It is interesting to note that the average dry-period duration of the infected cows in the above study was only 70 days (shorter than many New Zealand cows) yet there was still a benefit for the combination treated quarters in that environment.

	Infected cows				Uninfected cows			
	Cephalonium (no. of quarters = 830)		Cephalonium + teat sealant (no. of quarters = 831)		Teat sealant (no. of quarters = 777)		Teat sealant + cephalonium (no. of quarters = 779)	
	n	%	n	%	n	%	n	%
Streptococcus uberis	26	92.9	30	93.8	2	100	7	100
Escherichia coli	15	93.8	7	100	7	100	8	100
Aerococcus spp.	12	92.3	19	95	10	100	14	100
Coagulase-positive staphylococci	11	91.7	12	100	0	—	3	100
Enterococcus spp.	8	100	7	100	5	100	1	100
Bacillus spp.	4	100	6	100	4	100	2	100
Yeast spp.	1	25.0	0	—	0	—	0	—
Unspeciated gram-negative	3	100	5	100	4	100	3	100
Streptococcus spp.	3	100	5	100	4	100	2	100
Mucor spp.	2	100	1	100	0	—	0	—
Streptococcus dysgalactiae	2	100	4	100	0	—	0	—
Aspergillus spp.	1	100	3	100	0	—	0	—
Pseudomonas spp.	1	100	0	—	0	—	1	100
Arcanobacterium pyogenes	0	—	0	—	0	—	0	—
All *Enterobacteriaceae*	21	95.5	13	92.3	8	100	13	100
Staph./Strep. spp.*	50	92.6	56	94.9	11	84.6	13	100
Other major pathogens	2	100	2	100	5	100	8	100
All major pathogens	91	91.9	101	97.1	41	100	49	100

Table 2. Apparent dry cure rates for major pathogens in infected cows treated with cephalonium alone or cephalonium plus teat sealant and in uninfected cows treated with teat sealant alone (TS) or teat sealant in combination with cephalonium. Cows with the last 3 monthly individual SCC <200,000 cells/mL and no clinical mastitis within that period were allocated to the uninfected group and all other animals were allocated to the infected group.[26] n = number of infections at drying off that experienced a dry period cure; *coagulase-positive staphylococci and all *Streptococcus* species.

Expert's Concluding Comments

The control of mastitis is multifactorial and control strategies need to be tailored for each herd, herd manager, and farm owner as they will often have different or even competing goals. The value that different people attribute to their time and the costs they believe are attributable to mastitis do vary. In a seasonal calving dairy system, under which most of New Zealand's dairy cows are managed, having all of the cows dry at the same time presents an ideal time to control mastitis as the cycle of transmission can be stopped (at least for pathogens behaving in a contagious way) and the dry period is associated with good cure rates for subclinical infections. A well designed dry-cow therapy programme will get as many of the cows at the start of the following lactation with udders free of infection. To achieve infection-free udders at calving requires infected udders to be cured and for uninfected and cured udders to remain uninfected i.e. prevention of new infection. Cephalonium has been shown to have high cure rates and it will also provide greater protection against new infection than shorter-acting dry-cow therapy products.

Take-Home Messages

- Mastitis secondary to intramammary infection is a prevalent and costly disease for New Zealand farmers and the dairy industry as a whole.
- Not all measures that reduce economic losses due to mastitis are cost effective; dairy farmers should be provided with objective data on the additional expenditure and reduced losses associated with all available options.
- The dry period is the optimal time during the lactation cycle to remove existing intramammary infections.
- Selection of an appropriate antibiotic based on an individual herd's prevailing mastitis epidemiology and aetiology is important to achieve the highest rates of cure.
- Cephalonium in a long-acting base (Cepravin® Dry Cow) is a broad-spectrum antibiotic that has produced high mastitis cure rates in therapeutic intervention trials.
- Implementation of other mastitis control strategies is also important to ensure that high cures rates are converted to uninfected quarters at calving.

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