Comparison of tilmicosin and lincomycin/spectinomycin combination for treatment of footrot in merino sheep

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Abstract

This study was conducted on a commercial New Zealand sheep farm in order to compare the cure rates of merino sheep infected with footrot. Infected sheep were treated with either lincomycin/spectinomycin combination (Linco-Spectin soluble powder, Pfizer Animal Health) or tilmicosin (Micotil 300 Injection, ELANCO) antibiotics.

A flock of 3000 mixed age merino ewes had their feet inspected by the farm owner for the presence or absence of feet lesions. From these, 1200 mixed age merino ewes were inspected by the study investigator for the presence of active Grade 4 footrot. Feet lesions were graded (Appendix 1).

1076 sheep with active footrot (Grade 4) were identified and assigned to 1 of 2 treatment groups. 548 received a single intramuscular injection of Linco-Spectin combination (lincomycin 5mg/kg and spectinomycin 10mg/kg) as the positive control group. 528 were treated with a single, subcutaneous injection of Micotil 300 at a dose of 5mg/kg.

Subjects were then run together as a single mob. 15 days after treatment the feet of treated sheep were pared and re-inspected. A blinded assessment of each sheep was made. Feet were graded on the same footrot scale as previously, 0-4. A distinction was made between new cases of water maceration/ovine inter-digital dermatitis/early footrot infection (Grade 1-3) that had occurred since treatment, and active, chronic footrot infection (Grade 4) that had not responded to treatment.

CONCLUSION: (1) Merino sheep with Grade 4 footrot infection given a single treatment of tilmicosin at 5mg/kg, achieved significantly higher cure rate of that infection compared with sheep treated with a single treatment of lincomycin-spectinomycin. (98.3% versus 93.1% respectively, p value <0.0001). (2) The tilmicosin treatment group had significantly less new feet lesions occurring 15 days post-treatment compared with the lincomycin-spectinomycin treatment group (0.2% versus 9.6% respectively, p value <0.0001). (3) Overall the tilmicosin treatment group had significantly more uninfected feet 15 days after treatment compared with lincomycin-spectinomycin treatment group (98.3% versus 83.5 respectively, p value <0.0001).

Introduction

With respect to footrot in sheep, many sheep farmers are at worst, in a state despair and frustration, or at least annoyed at the sight of limping sheep. One of the main reasons many farmers will not consider fine wool production is because of the risks and hassles that footrot infection, perceived or previously experienced, possesses. Footrot infection is not however, just confined to fine wool, it is a considerable issue with many cross-bred flocks also and is an issue for terminal sire longevity.

Limitations to achieving footrot control lie in the areas of farmer attitude, degree of planning and advice received, having enough trained labour, suitable troughing and handling facilities, and the environmental conditions. There are a number of existing tools available that will reduce the pool of infection in a flock, but because the job of footrot control is not easy, it is natural to be looking for tools that can make faster and more comprehensive in-roads into fighting infection.

Footrot is costly to the sheep industry and is a concern on animal welfare grounds. A survey (Hickford *et al.* 2005) put the costs of footrot infection at 5% decrease in wool produced and 8% decrease in lambing percentage in New Zealand merinos. The total cost to NZ farmers annually was estimated to be $11million. An Australian trial showed an 11.6% reduction in body weight between footrot infected sheep and controls. An 8% (0.4kg) reduction in annual wool weight was measured in infected sheep compared to controls (Marshall *et al.* 1991).

Antibiotics remain a cornerstone for treating footrot (Vizard 1996, Jordan *et al.* 1996). Many thousands of doses are administered to sheep in New Zealand each year for the treatment of sheep lameness. The investigator's veterinary practice prescribed over 30,000 doses of antibiotics for the treatment of footrot in sheep in 2011. They are not "the silver bullet" for footrot and need to be prescribed as part of a footrot management plan, with an understanding of the stage of infection within a mob. For example, if prescribed during a spreading phase, cure rate is likely to be lower and re-infection rate higher.

Currently the use of Linco-Spectin Soluble Powder for the treatment of footrot in sheep is widespread (Venning *et al.* 1990). It contains a combination of lincomycin and spectinomycin. It achieves reasonable cure rates from a single dose (80-90%). The disadvantage of lincomycin-spectinomycin combination is that it is not registered for use in sheep in New Zealand. It comes in a powdered form registered for oral administration to poultry and swine, but is used as an off-label injectable product for footrot therapy in sheep. It is prescribed by veterinarians, and has a default meat withholding period of 91 days. It is mixed with sterile saline for the day of use and is recommended to be discarded if not used within 24 hrs of mixing. It is cheaper compared to other treatments (~$1.70/dose for a 55kg ewe). Penicillin has been a traditional antibiotic used for treatment of footrot, however to achieve reasonable cure rates higher doses than the label dose are required. Oxytetracycline is registered for use in sheep at a dose of 1mL/10kg and achieves reasonable cure rates, though more expensive than Linco-Spectin.

Micotil 300 injection (ELANCO animal health) is not currently available in New Zealand. It contains the active ingredient tilmicosin 300mg/ml. This is a member of the macrolide family, similar to lincomycin. It is registered for use in sheep in the United Kingdom for the treatment of respiratory disease and mastitis at a dose of 10mg/kg, and for footrot at a dose of 5mg/kg. It is registered in New Zealand for treatment of respiratory disease in cattle, and does not have any sheep treatment claims. The UK registered meat withholding period for Micotil 300 in sheep is 42 days. This study was conducted to confirm the efficacy of Micotil 300 against footrot in sheep under New Zealand commercial sheep farming conditions.

The study was conducted in accordance with the requirements of the ACVM Research Standard, and Animal Ethics Committee approval (Invermay # 12870).

Materials and methods

A clinical field effectiveness study, randomized design with positive control.

Treatment groups

Investigational product

Group A: Micotil 300 for Injection. Registered pursuant to the ACVM Act 1997, A6133. Administered subcutaneously. Dose 5mg/kg once (1ml per animal). 42 day meat withhold.

Positive control group

Linco-Spectin Soluble Powder treatment. Registered pursuant to the ACVM Act 1997, A2098. Combination dose of lincomycin 5mg/kg spectinomycin 10mg/kg. Mixed in saline and injected intramuscularly at 1ml /15kg (4ml per animal). Default meat withhold of 91 days. Off label use.

Randomisation method

Sheep were randomly assigned to treatment groups by alternate drafting prior to treatment.

Blinding/masking

Sheep were identified to treatment group using a spray marker on the top knot of the head. At the final assessment of clinical disease the treatment identification was not visible to the person making clinical disease assessments. The sheep were upside down at time of inspection. A second vet was involved with the assessment of clinical cure and was not aware of the treatment protocol.

Study animals remained at each study site under the direct management of the farm owner, as per routine management practice.

Study conduct

3000 commercial mixed age merino ewes weighing between 50-60 kg with five months wool growth were chosen. There was an ongoing footrot infection within the flock. A relatively large sample size was chosen to deliver statistical power to the data.

A specialized sheep handling conveyer was used to assist inspection of the feet on the first study visit. All four feet of each animal were inspected. Those with footrot infection present (as determined by the scoring system in section (Appendix 1) in at least one foot were drafted out. 1057 sheep were identified with footrot (Grade 4) and were enrolled. Animals were alternatively drafted into treatment groups. Antibiotic treatments were administered All tilmicosin (Micotil 300) treatments were administered by the study investigator wearing a specialized needle-proof glove on the non-injecting (left) hand. The Linco-spectin solution was administered by a trained operator under investigator supervision. Of the infected sheep (1057), 548 were treated with lincomycin-spectinomycin combination at the standard dose of 4ml. The other 528 were treated with tilmicosin (Micotil 300) 1ml. Each group was marked with a coloured spray, the tilmicosin group were marked red, the linco-spectin group were marked green and blue.

Fifteen days after initial antibiotic treatment the treated animals were tipped over through a sheep-feet inspecting chute and feet were inspected for presence of active footrot infection (Grade 4) and for new lesions (Grade 1-3) as per the previously described scoring system (Table 3). When re-inspecting the feet for cure, feet were pared using hoof trimmers, prior to grading of the lesions on the 0-4 scale. When determining clinical score of the feet, the veterinary assessors deemed any foot with moisture and/or exudates on the laminar surface of under-run hoof areas to still contain active footrot infection. On occasions the hoof was tested for the classic odour of active footrot.

Data handling and analysis

Data recording and record handling

As efficacy observations were made by assessors, a tally of animals was recorded for each category (Clear = score 0, Water maceration = score 1, ovine inter-digital dermatitis (OID) = score 2, OID+ plus early footrot = score 3,

active footrot = score 4). These records will form part of the final study records.

Statistical analysis

The main outcome was to measure cure rate of clinical footrot infection for each treatment group. The proportion cured from each group was t-tested for statistical significance.

Ho = > $pt_1 - pt_2 = Po$

H1 = > $p_1 - p_2 \neq Po$

Data was entered into the MiniTab programme. A t-test comparison between two groups was done to assess if the data groups were significantly different from each other to a 95% or 99% confidence interval (range of values which contains the population parameters). This t-test gives the P value (probability of obtaining an observed result) which allows an acceptance or rejection of the null hypothesis, i.e. that the two groups being compared are the same (Ho) or different (H1).

Test 1. Cure of initial infection

The number of sheep observed without active footrot (Grade 4) 15 days after treatment was compared between treatment groups.

The difference between the tilmicosin (micotil 300) treatment group cure rate (98.27%) was significantly greater than the linco-spectin group cure rate (93.14%) to the level of 99% confidence interval, P=0.0001.

Sample	X –cure rate of initial Infection	N- total in group	Sample P
1 Lincospectin group	502	539	0.931354
2 micotil group	510	519	0.982659
Estimate for p(1) –p(2)		-0.0513046	
95% CI for p(1) –p(2)		0.0754247 – 0.0271845	
Test for p(1) –p(2) =0 (v not =0)		Z= -4.17 P value 0.000	

Test 2. No active feet lesions 15 days after treatment

Fifteen days after treament the number of sheep with no active feet lesions was compared between treatment groups. The difference between the tilmicosin treatment group clean feet rate (98.07%) was significantly greater than the linco-spectin group clean feet rate (83.49%) to the level of 99% confidence interval, P =0.0001.

Sample	X –cure rate of footrot and no new lesions	N- total in group	Sample P
1 Lincospectin group	450	539	0.834879
2 micotil group	509	519	0.980732
Estimate for p(1) –p(2)		-0.145853	
95% CI for p(1) –p(2):		-0.179354, -0.112351	
Test for p(1) –p(2) =0 (v not =0):		Z= -8.53 P value 0.000	

Test 3. The proportion of new feet lesions (grade 1-3) 15 days after treatment

Fifteen days after treatment the number of sheep with new feet lesions (Grade 1-3) was compared between treatment groups.

The difference between the tilmicosin treatment group new lesion rate (0.20%) was significantly less than the linco-spectin group new lesion rate (9.6%) to the level of 99% confidence interval, P =0.0001.

Sample	X –New OID lesions occurring since treatment	N- total in group	Sample P
1 Lincospectin tx grp	52	539	0.103586
2 micotil tx grp	1	519	0.001961
Estimate for p(1) –p(2)		0.101625	
95% CI for p(1) –p(2)		0.0746935, 0.128556	
Test for p(1) –p(2) =0 (v not =0)		Z= 7.4 P value 0.000	

Results

Fifteen days post-treatment results of sheep with Grade 4 footrot treated with tilmicosin or lincomycin/spectinomycin combination.

Treatment group	No active infection	Active footrot (not completely cured due to treatment)	New feet lesions (Grade 1-3 occurring since treatment)	Cure rate of initial Grade 4 footrot
Lincomycin-spectinomycin combination (n=539)	450	37	52	93.1% (450+52/539)
	83.5%	6.9%	9.6%	
Micotil 300 (n=519)	509	9	1	98.3% (509+1/519)
	98.1%	1.8%	0.2	
P Value (99% CI)	<0.0001		<0.0001	<0.0001

Discussion

A single injection of tilmicosin (Micotil 300) was significantly better at curing footrot infection compared with single injection of Lincomycin-spectinomycin. Over 98% cure of footrot was achieved without any topical tough treatments or hoof paring. This is a significant finding. Australian best practice suggests cure rates of this nature were only achieved when sheep were footbathed post injection and kept on grating post treatment (Vizard 1996).

At the time of the first visit environmental conditions were dry and hot. (Appendix 2) Spread of the footrot infection had slowed. Between visits significant rain had fallen and morning dew was a regular occurrence. The increase in moisture was enough to allow water maceration and ovine inter-digital dermatitis to occur in some (9.6%) of the positive control animals with some of these cases having the beginning of a new footrot infection (lifting and under-run of hoof at the axial groove and heel). The significantly less number of new feet lesions in the tilmicosin treatment group suggests that the prolonged length of action of the product in the animal not only provides better cure of existing infection, but also can prevent the cycle of new infection (ovine inter-digital dermatitis) occurring

for at least 12 days.

Given the pharmacological properties of tilmicosin in sheep and these findings, it is evident that tilmicosin is a highly effective treatment for footrot infection and can break the cycle of re-infection in sheep in New Zealand field situations.

Attributable cure rate

The cure rate for each group did not consider the spontaneous or self cure rate. Obtaining the self-cure rate by having an untreated negative control group would have enabled the calculation of a cure rate directly attributable to antibiotic treatment (Vizard 1996). Previous studies overseas have shown the self cure rate to range between 19-45% (Webb Ware *et al.* 1994). Self cure rate depends on many environmental and host factors. The 15 day interval between treatment and re-inspection in the current study meant self-cure may not have had a great deal of impact on cure-rate.

Improving efficacy of antibiotic treatments

When using antibiotics it is recommended that treated sheep be foot bathed immediately post treatment and stood on dry surface, such as grating in a wool shed for 24 hours (Jordan *et al.* 1996). If foot bathing in zinc sulphate occurred during the study it would likely have increased cure rate in the treatment groups. Foot bathing would have slowed the development of ovine inter-digital dermatitis (OID) that was seen at re-inspection in the positive control group.

Treatment of animals with shorter acting antibiotics (such as linco-spectin) with no foot bathing may result in a proportion of infection not being cured and new infection can then re-establish and spread to other animals if conditions allow.

Whole flock treatment v inspection and treatment of clinical footrot cases

With cure rates approaching 99% and a prolonged length of action, tilmicosin has the ability to be used to eliminate footrot infection at the flock level. This has been demonstrated in the UK and Europe (pers comm.).

A standard approach to footrot control would be to apply the traditional method inspecting feet during a control phase, and making a clean mob, with measures put in place to ensure maintaining this clean status as the top priority –viz. troughed and put on pasture that has not had sheep for at least two weeks and monitored closely for breakdowns. This clean mob would then require two further inspections more than one month apart and after a challenge phase to check for further breakdowns. Two clear inspections are required to claim the mob is "free from footrot". All infected or suspect cases would be treated with tilmicosin. This mob would then be re-inspected 14 days later to assess cure rate from treatment. The few suspicious cases or non-responders would be isolated and culled.

An alternative protocol would be to treat all sheep in the flock or on the property, inspect 14 days post treatment and cull or retreat non-responders or suspicious cases. The property would then have to put in place risk management procedures to ensure infection does not re-appear (Mulvaney 2002). Anecdotal reports from the UK suggest this has been a highly effective way of getting rid of footrot at the flock level.

The consequences of *D. nodosus* infection entering a clean flock can be severe as there is very little natural immunity within the flock. The flock would ideally be closed, with no outside purchasing of stock. If sheep are brought onto the property, such as breeding rams, a quarantine injection of tilmicosin could be justified, along with a period in a quarantine area. Heightened awareness of biosecurity would be required. Boundary fences regularly inspected and maintained. Staff and neighbors made aware of protocols for dealing with stragglers.

This alternative protocol would not be appropriate in farm systems that could not meet these requirements to maintain the footrot/*D. nodosus* free status. Farms with crossbred and fine wool systems would be problematic.

When using any antibiotic for treatment of a disease it is important to consider issues of responsible and sustainable

use of that drug. This field trial has demonstrated that tilmicosin is currently highly effective against footrot infection. The veterinary and farming community has a great opportunity to use this drug for the improvement of sheep production and welfare, however we must deploy the use of it in conjunction with a farm specific planned approach to footrot management and/or eradication. It is the opinion of the author that getting tilmicosin into New Zealand for the use against footrot infection in sheep presents an opportunity for farmers to engage with veterinarians to design footrot management strategies. The dispensing of the drug should only be approved once a documented footrot management consultation, with an up-skilled veterinarian has been completed. The administration of the tilmicosin will be done by a veterinarian. These measures will ensure the best results are obtained and the drug is used responsibly.

Mitigation of human toxicity issues

Tilmicosin is a cardiotoxic drug to humans. For this reason tilmicosin is "vet only" in the UK and Europe. This status is set to continue in New Zealand.

Conclusions

1. Merino sheep with Grade 4 footrot infection given a single treatment of tilmicosin at 5mg/kg, achieved significantly higher cure rate compared with sheep treated with a single treatment of lincomycin-spectinomycin. (98.3% versus 93.1%, p value <0.0001).
2. The tilmicosin treatment group had significantly less new feet lesions occurring 15 days post- treatment compared with the lincomycin-spectinomycin treatment group (0.2% versus 9.6% p value <0.0001)
3. Overall the tilmicosin treatment group had significantly more non-infected feet 15 days after treatment compared with lincomycin-spectinomycin treatment group (98.3% versus 83.5%, p value <0.0001).

Tilmocosin should not be viewed as a silver bullet for footrot. Tilmicosin does have pharmacological properties that make it appear superior to current antibiotics. It would be a useful tool when prescribed as part of a whole-farm footrot control strategy. The introduction of this drug presents new opportunities for sheep veterinarians to engage with famers on footrot management issues.

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Appendix 1. Photo foot score grading

Description	Grade
No infection	0
Water maceration	1
Ovine interdigital dermatitis (OID)	2
OID plus early footrot	3
Active footrot	4

Appendix 2. Photos of tilmicosin v lincomycin-spectinomycin combination footrot trial. Hyde, March 2013

1.1 Trial ewes showing environmental conditions (visit 1).

1.1a Ewes on pasture after 1st visit.

1.2 & 1.2a First inspection of ewes prior to treatment.

1.3 Randomised, alternate drafting of ewes into 2 groups prior to treatment.

1.4 Ewes being treated in tandem race. Furtherest race tilmicosin group, closest race, linco-spectin group. Note needle proof glove on investigators left hand. Nic Richards (closest).

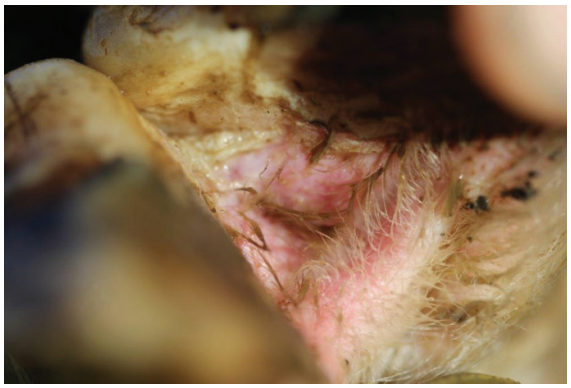
2.1 2nd visit to pare and inspect treated sheep for cure. Dave Robertson (investigator).

3.1.Hoof lesion grading system.

Grade 4. Advanced, active footrot

Grade 2. Ovine interdigital dermatitis (OID)

Grade 1. Water maceration – early OID



Grade 0. Non-infected hoof