OPEN ACCESS
DOI: 10.5455/javar.2015.b86

J. Adv. Vet. Anim. Res., 2(3): 279-284.
Available at- *http://bdvets.org/JAVAR*

JAVAR Journal of Advanced Veterinary and Animal Research

ORIGINAL ARTICLE

Volume 2 Issue 3 (September 2015)

Comparative efficacy of tulathromycin versus a combination of florfenicol-oxytetracycline in the treatment of undifferentiated respiratory disease in large numbers of sheep

Mohsen Champour[1,2,*] and Alinaghi Taghipour[2]

[1]*Department of Clinical Sciences, School of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran;*
[2]*Private practitioner, Mehr Animal Hospital, Garmsar, Garmsar, Iran.*
[*]*Corresponding author's e-mail: mchampour@yahoo.com*

ABSTRACT

The objective of this study was to compare the efficacy of tulathromycin (TUL) with a combination of florfenicol (FFC) and long-acting oxytetracycline (LAOTC) in the treatment of naturally occurring undifferentiated respiratory diseases in large numbers of sheep. In this study, seven natural outbreaks of sheep pneumonia in Garmsar, Iran were considered. From these outbreaks, 400 sheep exhibiting the signs of respiratory diseases were selected, and the sheep were randomly divided into two equal groups. The first group was treated with a single injection of TUL (dosed at 2.5 mg/kg body weight), and the second group was treated with concurrent injections of FFC (dosed at 40 mg/kg bwt) and LAOTC (dosed at 20 mg/kg bwt). In the first group, 186 (93%) sheep were found to be cured 5 days after the injection, and 14 (7%) sheep needed further treatment, of which 6 (3%) were cured, and 8 (4%) died. In the second group, 172 (86%) sheep were cured after the injections, but 28 (14%) sheep needed further treatment, of which 10 (5%) were cured, and 18 (9%) died. This study revealed that TUL was more efficacious as compared to the combined treatment using FFC and LAOTC. As the first report, this field trial describes the successful treatment of undifferentiated respiratory diseases in large numbers of sheep. Thus, TUL can be used for the treatment of undifferentiated respiratory diseases in sheep.

Keywords

Draxxin, Iran, Nuflor, Ovine, Oxipra, Pneumonia

ARTICLE HISTORY

Received : 3 May 2015, **Revised**: 11 May 2015,
Accepted : 11 May 2015, **Published online**: 12 May 2015.

INTRODUCTION

Respiratory diseases are common in cattle, sheep, goats, and other animals. Several microorganisms could be recovered from the respiratory tracts of the animals. In sheep, the problem is very common, and is responsible for enormous financial losses worldwide. In addition to the economic loss, high morbidity represents a significant animal welfare issue. Sheep pneumonia is regarded as a complex disease involving interactions between the host (immunological and physiological), multiple agents (bacteria, virus, mycoplasma, chlamydia, fungus and parasites) and environmental factors (Ackermann and Brogden, 2000). *Pasteurella multocida*, *Mannheimia haemolytica* and *Bibersteinia trehalosi* (formerly *M. haemolytica* serotype T) infections, often complicated by *Mycoplasma* colonization, are the most common causes of respiratory diseases in sheep and goats (Ackermann and Brogden, 2000; Zamri-Saad and Mera, 2001; Berge et al., 2006; Washburn et al., 2007).

Respiratory disease is characterized by depression, lack of appetite, fever, cough, nasal discharge, ocular discharge and dyspnea. Use of antimicrobial in sheep has long been recommended for the treatment of diseases relating to the respiratory tract (Christodoulopoulos et al., 2002). Several injectable antibacterials such as tilmicosin, florfenicol (FFC), oxytetracycline (OTC), tulathromycin (TUL) can be used for the treatment of the animals suffering from different respiratory diseases. However, to the best of our knowledge, no clinical report has been reported on the assessment of TUL on large scale basis. Therefore, this study was designed to compare the efficacy of TUL with a combination of FFC and long-acting

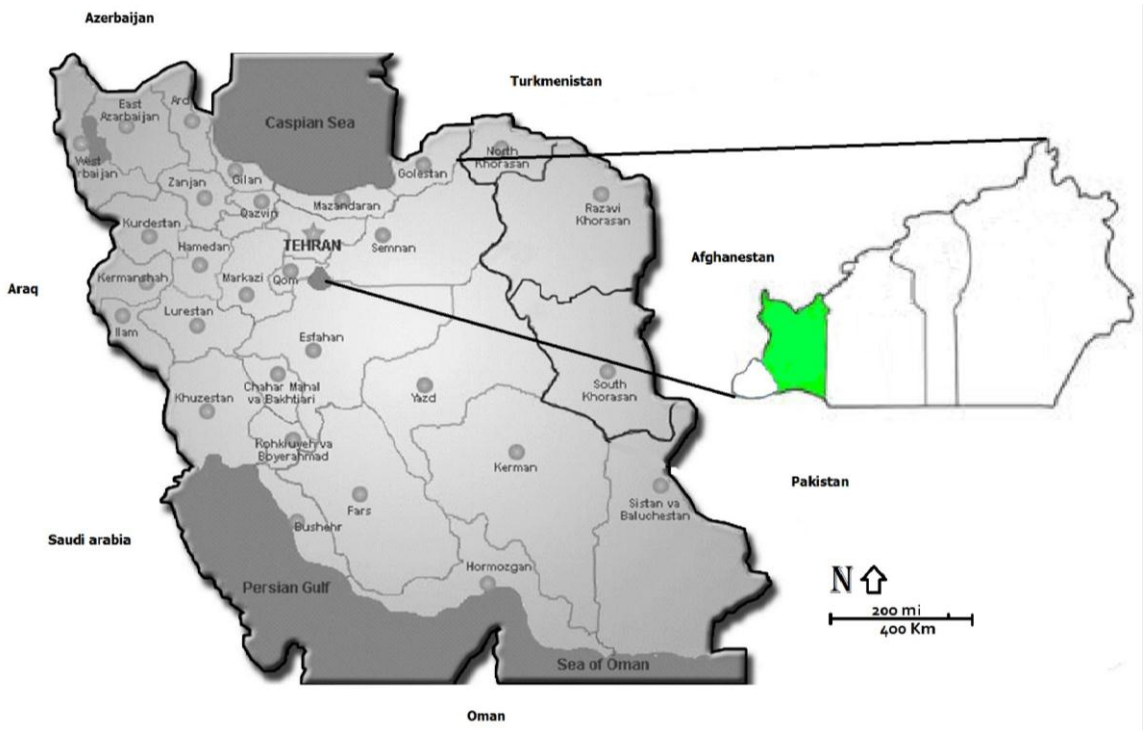

Figure 1. Study area in Iran map is shown with green color. The Garmsar is located approximately 120 km southeast of Tehran, Iran, at the southern fringe of the Alburz mountain range, where the Hableh Rud River emerges and where the Dasht-e-Kavir desert begins.

oxytetracycline (LAOTC) in the treatment of naturally occurring undifferentiated respiratory diseases in sheep.

MATERIALS AND METHODS

Study area: The study was carried out in the Garmsar area of Iran. The Garmsar is located approximately 120-km southeast of Tehran, Iran (**Figure 1**). The climate of the Garmsar area is continental arid, and rainfall and humidity are low. The average annual rainfall of this area is 100-120 mm, and rainfall occurs mainly from January to March. The summers are hot and the winters are cold, and the potential evaporation is high. Garmsar contains approximately 2,200,000 sheep; herd size varies from farm to farm, and the most common sheep breeds are Iranian Shal, Baluchi and Sangesar, and their cross breeds.

Sampling and tests: From April 2007 to September 2008, seven natural outbreaks of sheep pneumonia in separate herds were investigated. Four hundred sheep of both sexes that were approximately 6-9 months old and exhibited the following symptoms: depression, anorexia, cough, sneezing, conjunctivitis, ocular and nasal discharges, a body temperature greater than 39.5°C and a respiratory rate greater than 35/min, were selected. The sheep were randomly divided into two equal groups. The first group was treated with a single injection of TUL, and the second group was treated with concurrent single injections of FFC and LAOTC. The animals were carefully injected and every effort was made to minimize their discomfort, distress or pain; we assumed that any procedures that would cause pain in humans may cause pain in the study animals, and the procedures were conducted by experienced technicians. Tulathromycin (Draxxin®, Pfizer Animal Health) was given as a 10% solution; each milliliter contained 100 mg TUL and was administered subcutaneously at 2.5 mg/kg bwt. Long-acting oxytetracycline (OXIPRA® 20 L.A. HIPRA) was given as a 20% solution; each milliliter contained 200 mg oxytetracycline as hydro-chloride, and was administered intramuscularly at 20 mg/kg bwt. Florfenicol (Nuflor®, Schering-Plough Animal Health Corporation) was given as a 30% solution; each milliliter contained 300 mg FFC and was administered subcutaneously at 40 mg/kg bwt. All animals were checked at daily feeding times with expert vet. We assumed appetite as a sensitive indicator of successful treatment, so if the sheep continue to eat following drug injection it assumed as successful treatment and cured, but if appetite was not good or decreased subsequently we examined it for further clinical

parameter as like, the body temperature, respiratory rate and sounds, cough, ocular and nasal discharge, and then ranked it according to **Table 1**.

Statistical analysis: The data were analyzed by a Student's t-test and a Wilcoxon signed-rank test using the SPSS statistical package (version 20.0). Differences were considered to be statistically significant when $P<0.05$.

RESULTS AND DISCUSSION

The selected animals were examined one day before starting the treatment, and after 5, 10 and 20 days of starting treatment. In the TUL group, 186 (93%) sheep were cured 5 days after the first injection, and 14 (7%) needed further treatment, of which 6 (3%) were cured, and 8 (4%) were died. In the FFC-LAOTC group, 172 (86%) sheep were cured after the first injections, but 28 (14%) sheep needed further treatment, of which 10 (5%) sheep were cured and 18 (9%) were died. The mean body temperature (mean±SE) before treatment in the TUL group was 40.3±0.07°C, and after treatment it was 38.8±0.06°C, and in the FFC-LAOTC group, it was 40.5±0.06°C before and 39.0±0.06°C after treatment. Although body temperature on the first day after the injections did not differ significantly between the groups, it was significantly lower in the TUL group than in the FFC-LAOTC group 5 days after the injection ($P<0.05$). The clinical score, which was a mean value of the respiratory condition, nasal and ocular discharge and general condition, was not significantly different between the groups 5 days after the treatment, but it was significantly better in the TUL group 20 days after the injection (**Table 1, 2**).

Lesions were observed at the injection site (*i.e.*, swelling, local abscess and diffuse cellulitis) in 4 (2%) sheep in the TUL group and 6 (3%) in the FFC-LAOTC group; in the latter group, all the lesions were seen at the LAOTC injection site. There was no significant difference in lesion occurrence between the groups. The clinical signs before death were as follows: inappetence, lethargy and normal or subnormal body temperature. Post-mortem examinations revealed significant congestion, hyperemia, abscess and fibrous adhesive between the visceral and parietal pleura, particularly in the cranial lobes, and different patterns of pneumonia on the lung surface.

This study evaluated the efficacy of TUL and a combination of FFC-LAOTC for the treatment of respiratory disease in sheep. Several previous studies have established a clear link between the risk of respiratory diseases and decreased productivity in different species (Nanjiani et al., 2005; Clothier et al., 2012; Heins et al., 2014). TUL is a triamilide-macrolide agent that maintains therapeutic concentrations for an extended period of time. It is characterized by a rapid absorption from the injection site, extensive distribution to tissue and slow elimination, thereby providing a high, prolonged concentration in the lungs (Evans, 2005). This property of TUL may well explain why we obtained a very good outcome regarding body temperature 5 days after treatment, and also an excellent clinical score was found 20 days after treatment. TUL is approved for the treatment of bovine respiratory disease, infectious bovine keratoconjunctivitis, foot-rot in beef and non-lactating dairy cattle, and for the treatment and control of swine respiratory disease; it is also occasionally used in goats (Young et al., 2011; Clothier et al., 2012). However, due to lack of information, it has not been approved for use in sheep.

The treatment of pneumonia using OTC has been largely accepted; OTC is a wide-spectrum bacteriostatic antibiotic and acts against a large number of Gram-negative, Gram-positive, Rickettsia, Chlamydia and Mycoplasma infections. It is used for the treatment of local and systemic infections and possesses newly discovered additional properties, including anti-inflammatory and immunosuppressive activity (Olszewska, 2006). Among the tetracyclines, injectable LAOTC has the advantage of producing prolonged, high serum concentrations as compared to conventional oxytetracyclines. This property extends the interval between injections when treating clinical disease. According to our experiences, use of this agent as a single drug was not found as a good choice for treatment of undifferentiated respiratory disease in sheep; this result is in agreement with the findings of Giguere et al. (2013), and also we found that treatment with LAOTC was associated with a greater probability of requiring re-treatment in the 5-7 days following the initial therapy. In addition, we observed large numbers of agents that were resistant to LAOTC (data unpublished); therefore, we used it in combination with other antibiotics, in order to expand it's antibacterial range and to reduce bacterial resistance.

The FFC is a fluorinated thiamphenicol analogue and has been approved for the treatment of bovine respiratory diseases (Catry et al., 2008). The FFC is a broad-spectrum, primarily bacteriostatic antibiotic, with a range of activity that includes many Gram-negative and Gram-positive organisms. In our experience, FFC and LAOTC make an excellent

Table 1. Clinical scoring system designed for assessment of sheep.

Score	General attitude	Cough type	Ocular discharge	Nasal discharge
1	No abnormality	No cough	No discharge	No discharge
2	Slightly depress	A few, wet	Slightly, serous	Slightly, serous
3	Moderately depress	Multiple, harsh	Moderate, purulent	Moderate, purulent
4	Sever depress	Multiple, paroxysmal	Copious, purulent	Copious, purulent

Table 2. Average clinical scores of sheep in different days.

Clinical score	Before 1 day	After 5 days	After 10 days	After 20 days
General attitude FFC-LAOTC/TUL	3-3	1-1	2-1	2-1
Cough FFC-LAOTC/TUL	3-3	1-1	2-2	2-1
Ocular discharge FFC-LAOTC/TUL	3-3	1-1	1-1	1-1
Nasal discharge FFC-LAOTC/TUL	3-3	1-1	2-1	2-1

combination, which is a good choice for undifferentiated respiratory disease in sheep, particularly in situations in which there are no scope of doing bacterial sensitivity tests. Because this study was conducted during natural outbreaks, we were bound to select the drugs that would achieve the best outcome, and reduced the mortality rates; thus, we used this combination versus the novel use of TUL.

The etiology of the acute ovine respiratory disease described in the current study was undifferentiated; establishing the etiology was not a component of this study protocol, as ovine and bovine respiratory disease is a multi-factorial problem, and there is usually no simple microbiological pattern of infection (Ackermann and Brogden, 2000; Zamri-Saad and Mera, 2001; Berge et al., 2006; Washburn et al., 2007). An etiological approach to the diagnosis, treatment and control of ovine respiratory diseases is adopted in most review articles and book chapters; however, such precise classification is unrealistic in most general veterinary practice situations, because clinical signs are not pathognomonic for particular causative agents, costs limit laboratory resources to isolate the causal agents and necropsy findings are easily confused (Donachie, 2007; Bell, 2008).

In the present study, the body temperature in both groups returned to normal a day after the injection, and this finding is compatible with that found by Aytekin et al. (2010) in calves. The body temperature in the TUL group 5 days after injection was significantly lower than that in the FFC-LAOTC group (P<0.05). This may have been because pulmonary tissue accumulated high concentrations of TUL over an extended period, but FFC-LAOTC levels gradually depleted, and further injections were usually required. This result is in agreement with those from previous studies (Benchaoui et al., 2004; Evans, 2005).

The clinical score was not significantly different between the groups 5 days after treatment, but it was significantly better in the TUL group 20 days after the first injection. We strongly believe that the large number of animals that were treated with a single dose of FFC-LAOTC actually needed further doses, although the majority of these animals may have appeared healthy. However, relapses, or chronic, subclinical disease may remain in these sheep, which can inconspicuously affect their clinical scores.

The total cure rate in the TUL group was significantly greater than that in the FFC-LAOTC group (P<0.05). Similar results have been obtained by other investigators when they have compared TUL with different antibiotics for the treatment of respiratory disease in different animal species (Godinho et al., 2005; Nanjiani et al., 2005; Rooney et al., 2005; Clothier et al., 2012; Heins et al., 2014).

We observed lesions (swelling, local abscesses or diffuse cellulitis) at the injection site in less than 3% of the treated sheep; 4 (2%) in the TUL group and 6 (3%) in the FFC-LAOTC group, but the difference was not significant. The lesions had cleared by the time of the final examination, and there was no mortality related to them. This finding is not in accordance with the results of a study in calves (Aytekin et al., 2010), which did not find any significant adverse reaction in TUL-treated calves. It is possible that this may have been the result of the small number of calves used in that study (20 calves in each group), or it is possible that these lesions are species-specific. In our experience, such problems are more common in LAOTC-treated animals (e.g.

sheep, deer and cattle) and are partly caused by operator error or defective instruments (*e.g.*, conducting injections in a rainy climate, using one needle for a large group of animals, the use of blunt needles and the problem of suction when using automatic syringes). However, the problem is also related to the chemical nature or innate formulation of LAOTC, in particular, the newly discovered immune-suppressive activity of oxytetracycline (Olszewska, 2006); this immunosuppressive activity may predispose animals to local infections and further complications.

None of the treated sheep died of acute disease, because the clinical signs of disease after the treatment were mild or absent, so both drugs were effective in this regard. However, due to the chronic nature of the disease, or concurrent viral or mycoplasmal involvement, a small number of these animals were not cured. The clinical signs before death were inappet-ence, lethargy and normal or subnormal body temperature, and in the post-mortem examinations we observed significant congestion, hyperemia, abscesses, and fibrous adhesive between the visceral and parietal pleura, particularly in the cranial lobes, with different patterns of pneumonia, observed on the lung surface. We suggest that the dead animals contained viral or mycoplasmal agents, because these are more resistant to treatment, particularly in chronic cases, and this is in accordance with the results of Mdanat et al. (2001). This study found that, although the treatment of mycoplas-mosis is currently based on vaccination or antibiotics (such as tetracyclines, macrolides, FFC, tylosin and fluoroquinolones), the results of treatment may be poor or ineffective if the therapeutic dose is not well defined and the antibiotic is not administered for a sufficiently long period, or if the disease is chronic (Mdanat et al., 2001).

CONCLUSION

The results of the present study suggest that a single dose of tulathromycin (TUL) and a combination of FFC-LAOTC both are effective for the treatment of respiratory diseases in sheep, but the treatment using only TUL is better in terms of recovery rate. We suggest using TUL as the first injection, and in uncured animals, TUL can be considered for a second injection. The information obtained in the present study can also be used to provide predictive models for other species. Data from this study may also be useful in designing complete protocols for the studies to be conducted in sheep and other species, and facilitate adherence to the US Food and Drug Administration (FDA) requirements for the approval of the use of TUL in these species.

ACKNOWLEDGMENT

The authors greatly appreciate the assistance of staff members from the Mehr Food Animal Hospital, Garmsar, Iran for their technical supports.

REFERENCES

Ackermann MR, Brogden KA (2000). Response of the ruminant respiratory tract to *Mannheimia* (*Pasteurella*) *haemolytica*. Microbes and infections, 2: 1079-1088.

Aytekin I, Mamak N, Onmaz AC, Sakin F, Aslan S (2010). Effects of Tulathromycin and Tilmicosin Application in the Treatment of Bovine Respiratory Disease in Cattle. The journal of the Faculty of Veterinary Medicine University of Yuzuncu Yil (Turkish), 21: 159-162.

Bell S (2008). Respiratory disease in sheep. Journal of the British veterinary association, 30: 200-207.

Benchaoui HA, Nowakowski MA, Sherington J, Rowen TG, Sunderland SJ (2004). Pharmacokinetics and lung tissue concentrations of tulathromycin in swine. Journal of Veterinary Pharmacology and Therapeutics, 27: 203-210.

Berge AC, Sischo WM, Craigmill AL (2006). Antimicrobial susceptibility patterns of respiratory tract pathogens from sheep and goats. Journal of the American Veterinary Medical Association, 229: 1279-1281.

Catry B, Duchateau L, Van de Ven J, Laevens H, Opsomer G, Haesebrouck F, De Kruif A (2008). Efficacy of metaphylactic florfenicol therapy during natural outbreaks of bovine respiratory disease. Journal of Veterinary Pharmacology and Therapeutics, 31: 479-487.

Christodoulopoulos G, Warnick LD, Papaioannou N, Fthenakis GC (2002). Tilmicosin administration to young lambs with respiratory infection: safety and efficacy considerations. Journal of Veterinary Pharmacology and Therapeutics, 25: 393-397.

Clothier KA, Kinyon JM, Griffith RW (2012). Antimicrobial susceptibility patterns and sensitivity to tulathromycin in goat respiratory bacterial isolates. Veterinary Microbiology, 156: 178-182.

Donachie W (2007). Pasteurellosis, In: Aitken ID, editor. Diseases of sheep, 4th Edn., Oxford (UK): Blackwell Publishing; pp 224-235.

Evans NA (2005). Tulathromycin: an overview of a new triamilide antibiotic for livestock respiratory

disease. Veterinary Therapeutics: Research in Applied Veterinary Medicine, 6: 83-95.
Giguere S, Prescott JF, Dowling PM (2013). Antimicrobial Therapy in Veterinary Medicine. Fifth Edn., Wiley-Blackwell; pp 264-266.
Godinho KS, Rae A, Windsor GD, Tilt N, Rowan TG, Sunderland SJ (2005). Efficacy of tulathromycin in the treatment of bovine respiratory disease associated with induced *Mycoplasma bovis* infections in young dairy calves. Veterinary Therapeutics: Research in Applied Veterinary Medicine, 6: 96-112.
Heins BD, Nydam DV, Woolums AR, Berghaus RD, Overton MW (2014). Comparative efficacy of enrofloxacin and tulathromycin for treatment of preweaning respiratory disease in dairy heifers. Journal of Dairy Science, 97: 372-382.
Mdanat A, Zedulkova D, Pospisil Z (2001). Contagious agalactia of sheep and goats, a review. Acta Veterinaria Brno, 70: 403-412.
Nanjiani IA, Mc Kelvie J, Benchaoui HA, Godinho KS, Sherington J, Sunderland SJ, Weatherley AJ, Rowan TG (2005). Evaluation of the therapeutic activity of tulathromycin against swine respiratory disease on farms in Europe. Veterinary Therapeutics: Research in Applied Veterinary Medicine, 6: 203-213.
Olszewska, M (2006). Oxytetracycline-mechanism of action and application in skin diseases. Wiadomosci lekarskie (Warsaw, Poland: 1960), 59: 829-833.
Rooney KA, Nutsch RG, Skogerboe TL, Weigel DJ, Gajewski K, Kilgore WR (2005). Efficacy of tulathromycin compared with tilmicosin and florfenicol for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease. Veterinary Therapeutics: Research in Applied Veterinary Medicine, 6: 154-166.
Washburn KE, Bissett W, Fajt V, Clubb F, Fosgate GT, Libal M, Smyre KE, Cass KL (2007). The safety of tulathromycin administration in goats. Journal of Veterinary Pharmacology and Therapeutics, 30: 267-270.
Young G, Smith GW, Leavens TL, Wetzlich SE, Baynes RE, Mason SE, Riviere JE, Tell LA (2011). Pharmacokinetics of tulathromycin following subcutaneous administration in meat goats. Research in Veterinary Science, 90: 477-479.
Zamri-Saad M, Mera H (2001). The effect of *Pasteurella haemolytica* A2 infection on phagocytosis efficiency of caprine broncho-alveolar macrophages. Journal of Veterinary Medicine B, Infectious Disease and Veterinary Public Health, 48: 513-518.

****