Evaluation of the bioequivalence of two formulations of deltamethrin for treatment of sheep with psoroptic mange

Marie-Christine Cadiergues, DVM, PhD; Caroline Laguerre, DVM; Martine Roques, Michel Franc, DVM, PhD

Objective—To evaluate efficacy of 2 deltamethrin emulsifiable concentrates that differed on the basis of vehicle (methyl glycol acetate [AMG] or 2-propylene glycol 1-methyl ether acetate [AMP]) for the treatment of sheep with mange.

Animals—30 ewes between 11 months and 7 years old that weighed 16 to 71 kg and were naturally infested with *Psoroptes ovis*.

Procedure—Sheep were randomly allocated into 3 groups (13 sheep in group AMP, 13 sheep in group AMG, and 4 negative-control sheep). Each sheep was dipped twice (10-day interval between dippings) in the assigned formulation. Assessment of efficacy was performed on days 3, 7, 14, 21, 28, 35, 42, 49, 56, and 63 after the first dipping. Efficacy was assessed by determining the number of eggs or live mites on those days, as well as regrowth of wool at the end of the study.

Results—Psoroptic mange infestation was maintained in the 4 control sheep throughout the study. We did not detect live *Psoroptes* mites in scrapings after day 7 (AMP group) or after day 14 (AMG group). No parasites were seen after day 14 in either treatment group. Therefore, efficacy was 100% for both treatment groups from days 14 to 63.

Conclusions and Clinical Relevance—The 2 formulations of deltamethrin were equally able to eradicate *Psoroptes* infestation of sheep after 2 dippings performed in accordance with the label recommendations. (Am J Vet Res 2004;65:151–154)

Psoroptic mange of sheep is caused by *Psoroptes ovis* infestation and is a highly contagious parasitic disease responsible for large amounts of damage. Breeding and production performances are altered, and costs must be included for repair of damaged equipment. Dipping is the usual method for the prevention and treatment of sheep with mange.

Among the approved products, pyrethroids are often chosen for use.1,2 Deltamethrin is an ester of chrysanthemic acid and exists as the isomer 1R,Cis.3 It is a product for topical use that is ingested or absorbed (transcuticular absorption) by arthropods. It acts on sodium channels of the neuromuscular system of these parasites, causing the sodium channels to remain open for longer than is physiologically normal. This results in repetitive neural discharge and neurophysiologic disturbances that lead to behavioral changes and death.3 The compound has consistently had excellent activity for the control of arthropods parasitizing livestock and companion animals.

Deltamethrin is available in a number of registered formulations. The principle formulation is a 5% (wt:vol) emulsifiable concentrate that is sold commercially and has been available internationally as an ectoparasiticide for the past 18 years.

For regulatory reasons, it has become necessary for the manufacturer to replace the existing carrier (ie, methyl glycol acetate [AMG]) with another carrier (ie, 2-propylene glycol 1-methyl ether acetate [AMP]). Safety issues associated with this replacement carrier have been satisfactorily addressed, and the galenic properties of the replacement formulation are unchanged, compared with those properties for the current formulation. The objective of the study reported here was to determine whether there were detectable differences in the efficacy of the 2 formulations of deltamethrin attributable to the carrier when each was mixed with water and applied as a topical dip for the treatment of sheep with mange.

Materials and Methods

Animals and animal care—Thirty ewes that were between 11 months and 7 years old and weighed 16 to 71 kg were used in the study. Sheep were part of a commercial flock and were naturally infested with psoroptic mange. Sheep were randomly allocated into 3 groups (13 sheep in group AMP, 13 sheep in group AMG, and 4 negative-control sheep). All sheep were ranked on the basis of degree of infestation and then blocked and allocated at random to the groups. Each group was housed separately in isolated pens with solid walls (160 cm high × 14 cm thick), which were part of a breeze-block on a metal frame with a low-pitch roof that sloped from front to back. Each pen was approximately 26 m² and divided by a 220-cm high wall into 2 sections (approx 4 × 4 m [front section] and 4 × 2.3 m [back section]). Ventilation was provided by a vent (approx 60 cm) at the top of the roof in the area between the front and back section of the building and another vent (approx 40 cm) located at the junction of the roof with the front wall. Each pen could only be accessed from the front via a gate (80 cm wide × 170 cm high) that contained a metal grill mesh (5 cm²). A door separating the front and back sections of each pen was removed to allow free access to both sections of each pen at all times.

Each pen had a concrete floor. Pens were cleaned only on treatment days. Pens were bedded with straw after cleaning, and additional straw was added between cleanings when

Received June 5, 2003.
Accepted July 24, 2003.

From the UMR 181 Physiopathologie et Toxicologie Expérimentales INRA/ENVT (Cadiergues, Roques, Franc) and the Dermatology-Parasitology Unit, (Laguerre), Ecole Nationale Vétérinaire de Toulouse, 23, chemin des Capelles 31076 Toulouse cedex 3, France. Supported by a grant from Intervet Innovation GmbH.

The authors thank Rod Curtis, Cécile Caubet, Solange Vermot, and Cédric Petit for technical assistance.

Address correspondence to Dr. Cadiergues.
necessary. Sheep were fed hay and an additional commercial food. Drinking water was available ad libitum. The study was approved by an animal care and use committee.

Procedure—Sheep were allowed a 31-day acclimation period before the first treatment. Only female sheep confirmed to be infested with psoroptic mange were included in the study. All sheep had large numbers of *Psoroptes ovis* mites in skin scrapings obtained 7 days before onset of treatments.

Treatment—Sheep were treated with 1 of 2 formulations of deltamethrin (a formulation made with AMP [test treatment] and a formulation made with AMG [reference treatment]). Both were emulsifiable concentrates formulated for dilution with water and application by total immersion of sheep in a dipbath containing 5% (wt:vol) deltamethrin (ie, 50 mg/L). Each sheep was dipped twice (10-day interval between dippings) in the assigned formulation. Treatments were applied in an area in front of the animal pens by use of a mobile dip tank. Volume of the dip tank was 310 L, as calculated by use of a water flow meter.

Two fixed amounts of water were used in the dip tank. For medium-size sheep, 220 L of dipbath was used, whereas for large-size sheep, 250 L of dipbath was used. A glass cylinder was used to measure the appropriate amount of each formulation for the volume of dipbath. The formulation and water were mixed thoroughly with an electric stirrer before each sheep was dipped. Investigators were protective clothing in accordance with label recommendations when handling the concentrates. Investigators were aware of the treatment applied to each sheep. Each sheep was dipped separately and kept in the dipbath for 1 minute; the head of each sheep was immersed briefly but completely 2 or 3 times. Sheep in the control group were not immersed in the tank.

After each sheep was dipped, the tank was emptied and filled with fresh water and deltamethrin prior to treatment of the next sheep. The tank was emptied and cleaned by use of a series of water rinses between treatment groups.

During each treatment procedure, the pens were cleaned, and existing straw and hay were removed. The pens and feed rack were washed by use of a high-pressure washer. Fresh straw and hay were then put into the pens prior to return of the sheep.

Efficacy and safety assessments—Assessment of safety was performed by daily observation of all sheep throughout the study. Assessment of efficacy was performed on days 3, 7, 14, 21, 28, 35, 42, 49, 56, and 63 after the first dipping for all sheep in the 2 treatment groups. Efficacy was determined on the basis of the number of eggs or live mites on those days, as well as regrowth of wool at the end of the study. For the purpose of ensuring that mange would have persisted in untreated sheep, these variables were also assessed at the same time points in the untreated control group.

Two skin scrapings were obtained from the woolled area on each side of each sheep. Samples were placed in plastic vials and subsequently examined in our laboratory. Each scraping was weighed and then washed with warm soapy water. Wool and crusts were separated from the liquid fraction by use of a fine mesh. Microscopic examinations of liquid, wool, and crust components were conducted separately. The number of live *Psoroptes* mites per gram of material was calculated.

Skin scrapings were also obtained from nonwooled areas (ie, pinna of each ear, each infraorbital fossa, each foot, and each side of the vulva). These scrapings were processed and examined as described previously.

Investigators who evaluated the skin scrapings were not aware of the treatment applied to each sheep. Scrapings for each area were scored on a scale of 0 to 10 (0, no parasites detected; 0.5, 1 to 10 *Psoroptes* mites detected; or 1, >10 *Psoroptes* mites detected). Total score was the mean number of *Psoroptes* mites per gram of skin scraping from the 4 woolled areas plus 10 times the score obtained for the nonwooled areas.

Data analysis—Primary efficacy was determined by use of the following equation: 

$$\text{efficacy} = \left(\frac{\text{number of treated sheep} - \text{number of sheep still infested}}{\text{number of treated sheep}}\right) \times 100$$

Cure rates were based on the efficacy determined by use of this equation. Sheep that did not have any mites at the end of the study period were considered cured. When mites were still evident on a specific treatment day, that sheep was considered still infested on that day.

Our primary interest was to compare efficacy of the 2 treatment formulations. Treatment with the AMP formulation (test treatment) was regarded as efficacious when there was therapeutic equivalence of the cure rates for both treatments. When efficacy for either of the treatments was <80%, testing would not be performed because the treatment would be regarded as ineffective and equivalence could not be proven. In the situation in which efficacy was 100% for both treatment groups, a test for therapeutic equivalence would not be necessary because therapeutic equivalence would be assumed. When efficacy for both treatment groups was >80% but efficacy was <100% in 1 or both treatment groups, a test on therapeutic equivalence of cure rates would be performed by use of a test procedure derived from the Fisher exact test with a continuity correction.

Results

Clinical examination—None of the sheep had signs of poor health or adverse events during the study.

*Psoroptes* populations before treatment—All sheep had large numbers of *Psoroptes ovis* mites in the skin scrapings obtained 7 days before treatments. Mean number of live *Psoroptes* mites was 76 *Psoroptes* mites/g in the control group, 251 *Psoroptes* mites/g.
for the AMG group, and 306 Psoroptes mites/g for the AMP group (Fig 1). Scores in nonwooled areas for the control, AMG, and AMP groups were 8.6, 9.9, and 9.7, respectively (Fig 2). Total scores (wooled and nonwooled areas) for the control, AMG, and AMP groups were 162.0, 349.5, and 402.8, respectively (Fig 3). Values for the variables did not differ significantly between the 2 treatment groups. Because the control group was used to verify maintenance of infestation, we did not make comparisons between values for the treatment groups and the control group.

**Psoroptes populations after treatment**—Psoroptic mange infestation was maintained in the 4 control sheep throughout the study. Mean number of live Psoroptes mites ranged from 22 (day 35) to 98 (day 14). Scores for nonwooled areas ranged from 7.3 (day 63) to 10.0 (day 7). Total scores ranged from 102.0 (day 35) to 195.8 (day 14). A unique difference between the control group and treatment groups was the relative surface area of the pen for each sheep (ie, by design, there were only 4 untreated sheep).

We did not detect live Psoroptes mites in skin scrapings obtained after day 7 for the AMP group and after day 14 for the AMG group. Parasites were not seen in scrapings obtained from nonwooled areas after day 14 for either treatment group. Therefore, total score was 0 for day 14 until the end of the study for both treatment groups, and efficacy was 100% from day 14 to day 63.

**Discussion**

Infestation of the control sheep did not change throughout the study, whereas the number of mites in sheep of the respective treatment groups decreased dramatically. All control sheep were still infested at the end of the study, despite a lower initial number of mites and a larger pen surface area for each sheep, compared with those of the treatment groups. However, sheep with a lower initial number of mites were assigned to the control group because we wanted to minimize the consequences of mange on their health.

We documented here that the 2 formulations were equally able to eradicate psoroptic infestation from sheep after 2 dippings performed in accordance with the commercial label recommendations. The efficacy was extremely good: we did not detect *Psoroptes* mites or eggs of mites after the second dipping. In addition, live parasites were not found in samples obtained 63 days after the first dipping (a period of approx 5 egg-to-egg cycles for psoroptic mange mites). Furthermore, the products were tolerated well by the sheep. We did not detect signs of irritation while handling the sheep during dipping or when monitoring the sheep thereafter.

Analysis of results of the study reported here also confirms the necessity of 2 dippings because live *Psoroptes* mites were still detected on day 7 after the first treatment for both formulations. We also confirmed the necessity of keeping sheep in the dip tank for 1 minute and immersing each sheep's head briefly but completely 2 or 3 times. It is also essential to replenish the dip tank with the acaricidal product because of the lipophilic properties of the active ingredient, which affixes to the skin of the sheep.

Compared with other systemically administered treatments, dipping is an expensive method, but it is suitable for large flocks in which personnel want to avoid handling each sheep. Furthermore, the withdrawal period of deltamethrin administered via dipping (3 days for meat and offal; 0 days for milk) is reduced, compared with the withdrawal time after administration of injectable products such as ivermectin, moxidectin, or doramectin, which are not permitted for use
in lactating animals producing milk for human consumption and that have long withdrawal periods for meat and offal (21 days for ivermectin and 56 days for doramectin administered SC). Finally, dipping allows management of biting lice (*Damalinia ovis*) and chorioptic mange (*Chorioptes ovis*) that are not reached by other systemically administered products.6-8

References


