

The efficacy of a slow-release albendazole capsule against *Haemonchus contortus* with known resistance to albendazole

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Controlled-release albendazole capsules (CRCs) are currently registered for use in Australia and New Zealand as anthelmintic treatment in sheep. However, reports on the efficacy of such products on resistant parasite populations are sometimes controversial. This is the first study to report on the efficacy of such products under South African field conditions in sheep harbouring a population of *Haemonchus contortus* with known multiple anthelmintic resistance, including to albendazole. Treatment groups were comprised of CRC-treated and single dose albendazole-treated sheep, as well as negative controls. Groups were compared by using faecal egg count reduction tests, FAMACHA[®] anaemia scoring, conception rates and comparative weight gains over three and a half months. Based on a comparison of faecal egg counts, no advantage could be found using CRCs. Moreover, the use of the product actually decreased weight gain when compared with the control group animals.

Introduction

Worldwide, anthelmintic resistance is a major problem in the livestock industry. Against this background, novel compound discovery, combinations, methods of delivery, parasite management programmes and even vaccinations have been actively researched in order to make livestock farming more profitable, or in severe cases, even possible. In South Africa, the situation regarding haemonchosis is no exception (Van Wyk & Bath 2002; Van Wyk, Malan & Randles 1997).

The controlled-release capsule (CRC) is a tool that has been developed to extend the efficacy of anthelmintics after treatment. Theoretically, this would lead to longer treatment intervals with accompanying reduced stress to animals and labour costs. The effects on resistant helminths or the development of resistance to such a product is less clear. Previous reports have indicated conflicting results as to the efficacy of the sustained-released anthelmintics against resistant parasites (Sutherland *et al.* 1998). One such product registered for use in Australia and New Zealand is a 35% m/m albendazole sustained-release capsule (Extender 100[®], Merial, New Zealand) that can provide 100 days of continuous protection against susceptible strains of *Haemonchus contortus* (*H. contortus*) (according to the product's package insert).

In this study, the authors aimed to investigate the level of efficacy of sustained-release albendazole capsules for the first time in South Africa. However, as opposed to the label information that claims efficacy against susceptible helminth populations, this product was evaluated on a field strain of *H. contortus* in which multiple anthelmintic resistance had been recognised previously. The aim was to establish how such a product might affect the control of resistant parasites in a farming situation.

Materials and methods

Experimental design and randomisation

The trial was conducted as a positive and negative controlled field efficacy study of CRC albendazole against resistant *H. contortus* in sheep. Faecal egg counts (FEC) were compared between sheep treated with Extender 100[®] capsules and a negative and positive control group.

On 29 March 2011, a week after the egg per gram (EPG) count on a pooled flock sample reached 3300, treatment commenced (day 0). On this day, all animals were weighed, ranked by weight, and randomly allocated into treatment groups. Additionally, faecal samples were collected, FAMACHA[®] scores were assigned (see below) and treatment was given.

Two hundred maiden ewes were randomly allocated into treatment, positive control and negative control groups by sorting them alternatively through a swing gate (Table 1). The treatment group

TABLE 1: Summary of the study design.

Study group	Sub group	Treatment product	Subgroup <i>n</i>	Total <i>n</i>
Negative control	Individual faecal samples	None	50	85
	Bulk faecal samples	None	35	-
Positive control	-	Valbazen (single dose albendazole)	-	15
Treated group	Individual faecal samples	-	50	100
	Bulk faecal samples	-	50	-

n, number of animals

TABLE 2: Summary of the efficacy of various registered anthelmintics against the Stutterheim strain of *H. contortus* during 2005.

Compounds	Trade name	% egg count reduction
Albendazole + Levamisole + Ivermectin	Triton (Merial)	-31%
Albendazole + Closantel	Valbantel (Pfizer)	13%
Rafoxanide	Ranox (Pfizer)	-40%
Morantel	Banminth II (Pfizer)	-37%
Levamisole	Tramisol (Afrivet)	38%
Albendazole	Valbazen (Pfizer)	-8%
Doramectin	Dectomax (Pfizer)	-16%
Moxidectin†	Cydectin (Pfizer)	13%

†. The moxidectin data were from a survey (A.D. Fisher, 2007 unpublished data).

Note: Minus scores indicate that the faecal egg counts actually rose by that percentage in the faecal egg count reduction test.

consisted of 100 animals, the negative control group of 85 animals and the positive control group of 15 animals. In the treatment group, two further subgroups were created: 50 animals from which individual faecal samples were collected and 50 animals from which only pooled faecal samples were used for faecal analysis. Similarly, in the control group, two subgroups were created by randomly assigning animals: 50 animals from which individual faecal sample EPG counts would be done and 35 animals that contributed to a pooled faecal sample for EPG counts.

Each animal in the treatment group received a CRC (Extender 100[®], 35% m/m albendazole). The 15 positive control animals each received a standard oral dose (2 mL per 10 kg body weight) of a commercially available short-acting albendazole (Valbazen 1.9% m/v, Pfizer Animal Health, South Africa), whilst negative animals were left untreated.

Further faecal sample examination and FAMACHA[®] scoring was done every 14 days throughout the study until the termination of the animal phase of the study on day 99 after treatment commenced.

Study animals

Before inclusion in the study, 200 Dohne merino ewes, which were 18 months of age and weighed between 35 kg and 50 kg, were clinically examined by a veterinarian and found to be healthy.

Study site

All the study animals originated from and remained on the same farm for the duration of the study, which is located in the Stutterheim area of the Eastern Cape Province of South Africa (32°38'00"S and 27°35'32"E), a high summer rainfall area. The animals remained in the same camp during the

study and were thus exposed to the same natural grazing (mixed sourveld) and parasite burden. In addition, all animals were exposed to the same routine procedures for the duration of the study, which included mating 49 days to 91 days after commencement of the trial.

Parasite details

The *H. contortus* strain involved on this farm is known as the Stutterheim strain (also Kei road Strain or Robbie Blaine Strain) and has been used previously to test anthelmintics with an efficacy claim against resistant *H. contortus* (Little *et al.* 2011). In earlier trials performed on this farm during 2005 and 2007, FEC reduction tests revealed resistance patterns (as summarised in Table 2). In addition, faecal cultures from previous and subsequent trials (performed according to Reinecke 1983) revealed that the roundworm eggs that were produced were 100% *H. contortus* (Fisher 2013).

Faecal egg counts

Faecal processing and egg counts (modified McMaster method [Reinecke 1983]) were performed blindly by technicians at the Provincial Veterinary Laboratory, Queenstown, South Africa. For the bulk sample analyses, the FEC were performed three times and the average was taken.

FAMACHA[®]

From day 0 FAMACHA[®] was performed on all study animals approximately every fortnight. FAMACHA[®] is a method of selective treatment of sheep whereby only animals with the conjunctival mucous membranes displaying a certain degree of anaemia, as judged by a colour guide chart, are treated. Animals are subsequently divided into five groups based on their anaemia score: a score of 1 having pink-red mucous membrane colour and not requiring treatment for haemonchosis, to a score of 5 meaning that an animal has white mucous membranes, requires immediate treatment for haemonchosis and probable intensive medical treatment (Bath, Malan & Van Wyk 1996; Van Wyk & Bath 2002).

Analysis of trial results

The efficacy of the treatment was calculated using arithmetic group means in the following formula (McKenna 2006):

$$\% \text{ Efficacy} = 100 (1 - [T_{\text{after}}/T_{\text{before}}] \times [C_{\text{before}}/C_{\text{after}}]) \quad [\text{Eqn 1}]$$

T is the mean egg count of treated animals; before refers to day 0 and after to the specific day after the treatment date; *C* is the mean egg count of untreated controls.

Arithmetic means were used in the calculations of efficacy, as recent simulations have shown arithmetic means to give more accurate estimations of efficacy than logarithmic means (Dobson *et al.* 2009). FECs at different time periods were not compared with Repeated Measures Analysis of Variance as the assumption of sphericity among variances was not met. Thus, the non-parametric Kruskal-Wallis test (Kruskal & Wallis 1952) was performed at each time period. Proportions of animals showing different EPG values were evaluated with a chi-square test for an $r \times k$ contingency table.

Results

The efficacy results are shown in Table 3. Apart from day 30 post treatment (35.4% efficacy), there did not seem to be any efficacy of the product when individual animal FEC samples were compared. Furthermore, the Kruskal-Wallis test revealed that the only significant difference in FEC between groups existed at day 15 after treatment ($H(3) = 16.36, p < 0.001$), at which time the single treatment albendazole group had an efficacy of 83.6% (Table 3). The bulk FEC samples revealed a slightly longer duration of effect, albeit not satisfactorily effective ($< 90.0\%$). By the end of the trial, various animals had a zero eggs per gram faecal count: 31 (62.0%) in the individually sampled CRC treated group, 38 (76.0%) in the individually sampled negative control subgroup and 9 (60.0%) in the positive control group. The zero EPG rate was independent of the treatment group that the animal belonged to ($\chi^2_{(2)} = 2.73, p = 0.26$).

None of the sheep included in the study showed signs of severe helminthosis requiring anthelmintic treatment according to the FAMACHA[®] evaluation. The median FAMACHA[®] scores were the same for all the groups at every time period measured (median = 1). Similarly, conception results did not differ between CRC and untreated sheep ($\chi^2_{(1)} = 0.001, p = 0.97$). However, there was a significant effect of the type of treatment on the weight gain in the sheep (Table 4; $F_{(2,196)} = 7.46, p < 0.05$). Multiple comparisons using Bonferroni adjustment revealed that the untreated control

group had significantly higher weight gains than the group treated with the Extender 100[®] capsule. There was, however, no significant difference in weight gain between the negative (untreated) and positive (Valbazen) control groups.

Discussion

Extender 100[®] capsules are currently registered in Australia and New Zealand for treatment against susceptible populations of *H. contortus*. This study investigated the efficacy of sustained-release anthelmintics on resistant *H. contortus* infections.

Contrary to what previous studies have suggested (Fisher, Jacobs & Jones 1992; Le Jambre *et al.* 1981), but similar to Sutherland *et al.* (1998), no advantage was found according to faecal egg counts of sheep treated with sustained released albendazole compared with either single treatment albendazole or untreated controls when infected with resistant *H. contortus*. Interestingly, the short-acting albendazole combination had reverted back to 83.6% effectivity (moderately effective as described by Wood *et al.* 1995) from the -8.0% efficacy measured six years before the study. Although it is encouraging to learn the extent to which albendazole resistance appears to have been reversed on this farm, it is far less positive for the use of slow-release capsules.

Interestingly, the CRC treated sheep had a lower weight gain over the study period compared with untreated animals, similar to findings of Kelly, Walkden-Brown and Kahn (2012) and Williamson (1995). No previous report has attempted to explain this effect, but it may perhaps be related to larval mucosal stages inhibited by sustained release albendazole causing reduced abomasal function or perhaps even the physical presence of a capsule interfering with normal rumen function.

A few sheep reached peak FEC of 8600 eggs per gram by weeks two to four, but no sheep ever reached a FAMACHA[®] score of 3–5 requiring treatment for worms either during or

TABLE 3: Summary of efficacy calculated over the length of the study.

Groups compared	D 15 (13 April)	D 30 (28 Apr)	D 43 (11 May)	D 59 (27 May)	D 78 (15 June)	D 99 (06 July)
Efficacy ICRC vs IUC	-36.1	35.4	-97.7	-36.5	-88.9	-242.1
Efficacy ICRC vs ITC	-503.6	-31	-43.5	-21	-0.5	-177.6
Efficacy BCRC vs BUC	-36.3	51.4	23.6	23.6	59	79.5
Efficacy ITC vs IUC	83.6	24.7	31.2	18.4	1.8	64.4

Note: The efficacies are expressed in percentages.

D, study day since treatment on day 0; ICRC, individual (unpooled) egg per gram counts of controlled-release capsule treated sheep; IUC, individual (unpooled) egg per gram counts of untreated (negative) control group sheep; ITC, individual (unpooled) egg per gram counts of treated (positive) control group sheep; BCRC, bulk (pooled) egg per gram counts of controlled-release capsule treated sheep; BUC, bulk (pooled) egg per gram counts of untreated (negative) control group sheep

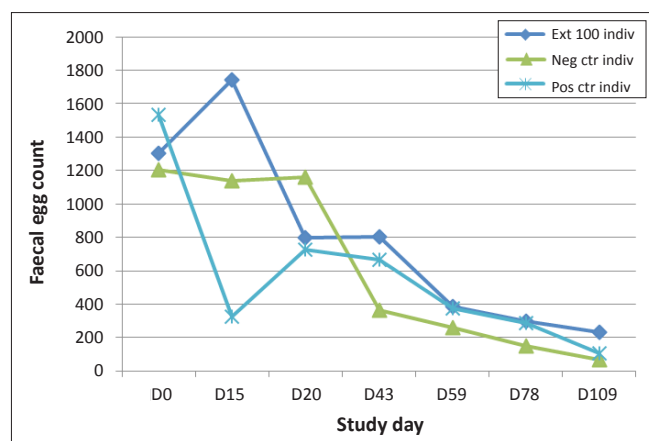
TABLE 4: Mean weight gains (kg) over the study period.

Treatment group	N	Mean	Standard deviation	Standard error	95% Confidence interval for mean	
					Lower bound	Upper bound
No treatment	85	5.1	1.5	0.2	4.7	5.4
Extender 100 ^{®a}	99	4.1	1.8	0.2	3.8	4.5
Valbazen	15	4.5	1.6	0.4	3.7	5.4
Total	199	4.6	1.7	0.1	4.3	4.8

^a, Has only 99 animals in sample as one animal was treated with a macrocyclic lactone because of *Chrysomayia bezziana* infection.

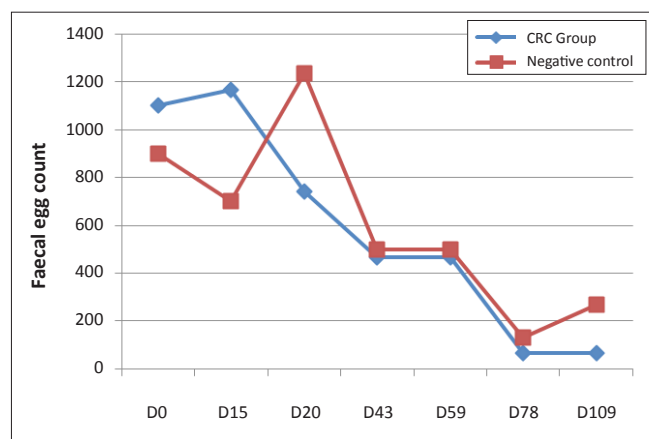
after the trial. Furthermore, the median FAMACHA® score in all groups in this study was 1. It is believed that this could be explained by the farmer actively selecting for internal-parasite-resilient sheep over many years. Drenching has been largely ineffective on this farm for many years due to resistance to virtually all of the active ingredients available until fairly recently. In addition, FAMACHA® scoring has been routinely employed since the emergence of resistance on the farm and is used with faecal egg counts to decide when to drench, if at all. All poor doers (generally due to high worm burdens and susceptibility to internal parasites) have been culled out of the flock. It is hypothesised that this strategy may have been responsible for the relatively quick reversion to moderate albendazole susceptibility of the *H. contortus* population.

Sheep in all groups in the trial showed a steady drop in faecal egg counts from mid-April until the end of the trial on 06 July (Figure 1 and Figure 2). This was attributed to a combination of: a reduction in the natural (field) challenge of *H. contortus* caused by cooler average daily temperatures in autumn and early winter; protein supplementation prior to mating; development of natural immunity to the worms after exposure; shedding of worms; and *H. contortus* becoming hypobiotic as winter approached. A previous report (Sutherland *et al.* 1998)



D, day; Ext 100 indiv, Extender 100® controlled-release capsule treated sheep; Neg ctr indiv, negative (untreated) control group sheep; Pos ctr indiv, positive (single oral albendazole dose) treated sheep

FIGURE 1: The arithmetic mean faecal egg count scores of individual animals (unpooled).



D, day; CRC group, Extender 100® controlled-release capsule treated group

FIGURE 2: Mean bulk (pooled) faecal egg counts of two groups during the study.

indicated that resistant strains of *Ostertagia circumcincta* and *Trichostrongylus colubriformis* established infection in CRC-treated animals and the humoral immune response to these parasites was not inhibited in CRC treated animals. Although this case involved a different parasite, it can be reported that the zero EPG value was not different between CRC and negative control groups, which could indicate similar levels of natural immunity developing in CRC treated animals and negative controls. However, this effect is difficult to separate from the effect of hypobiosis, as mentioned above.

Conclusion

In this trial, the slow-release 100 day albendazole capsule Extender 100® had no beneficial effect on resistant *H. contortus* parasite burdens as measured by faecal egg count and FAMACHA® scores, as well as on weight gain and conception rate.

Based on the results of this trial, the use of this product on farms with known severe albendazole resistance is probably contraindicated as it will possibly exacerbate the existing anthelmintic resistance problem by selecting for resistant worms, without any positive benefit to the sheep or owner.

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Competing interests

The authors declare that they have no financial or personal relationships that may have influenced them inappropriately in writing this article.

Authors' contributions

A.D.F. (Eastern Cape Department of Rural Development and Agrarian Reform, Provincial Veterinary Laboratory, Queenstown) was the project leader and was responsible for the experimental design, overseeing and/or performing all experimental work and writing the first draft manuscript. S.J.v.S. (MSD Malelane Research Unit, Malelane) made conceptual contributions and expanded the manuscript, performed the literature study and performed statistical analysis of the data.

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