Braz. J. Vet. Parasitol., Jaboticabal, v. 26, n. 4, p. 427-432, oct.-dec. 2017
ISSN 0103-846X (Print) / ISSN 1984-2961 (Electronic)
Doi: http://dx.doi.org/10.1590/S1984-29612017058

Multiple anthelmintic resistance in Southern Brazil sheep flocks

Múltipla resistência anti-helmíntica em rebanhos ovinos no sul do Brasil

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Received June 21, 2017
Accepted September 12, 2017

Abstract

Gastrointestinal parasites represent an important cause of reduced productivity of sheep worldwide. As anthelmintic are still the main control tool for these parasites, this work evaluated the efficacy of commercially available active principles in 22 sheep flocks in the southern region of Rio Grande do Sul, Brazil. In each farm 10 sheep were randomly distributed in seven groups with the following treatments: abamectin; albendazole; closantel; levamisole; monepantel; trichlorphon and no anthelmintic (control). All flocks showed resistance to at least three anthelmintics and in 20 farms only two products demonstrated efficacy for parasitic control. In two farms, there was no susceptibility to the six active principles tested. The results of this study provide evidence that the common commercially available anthelmintic are not assuring effective chemical control of gastrointestinal parasitic infections in ovine flocks in the southern region of Rio Grande do Sul. Monepantel, the newest introduced drug in the Brazilian market was not effective in 18% of the flocks tested, confirming that the parasitic resistance can be established quickly after the introduction of new molecules mainly when alternative program of parasite control is not performed.

Keywords: Sheep breeding, gastrointestinal nematodes, chemical control, resistance.

Resumo

As parasitoses gastrintestinais representam importante causa de queda na produtividade na ovinocultura mundial. Como a utilização de anti-helmínticos é, ainda, a principal forma de controle parasitário, o presente estudo avaliou a eficácia de princípios ativos comercialmente disponíveis, em 22 rebanhos ovinos da região Sul do Rio Grande do Sul, Brasil. Em cada propriedade foram utilizados 10 ovinos divididos em sete grupos que receberam os seguintes tratamentos: abamectina; albendazole; closantel; levamisole; monepantel; e triclorfon. Um grupo permaneceu como controle, sem tratamento anti-helmíntico. Nas 22 propriedades do estudo houve resistência, no mínimo, a três anti-helmínticos. Em 20 propriedades apenas dois produtos demonstraram eficácia para o controle parasitário. Em duas propriedades não houve sensibilidade aos seis princípios ativos testados. Os resultados do presente estudo demonstraram que os anti-helmínticos disponíveis no marcado Brasileiro não asseguram um controle parasitário efetivo nos rebanhos ovinos da região Sul do Rio Grande do Sul, incluindo o monepantel que foi ineficaz em 18% dos rebanhos testados, confirmando que a resistência dos parasitos aos princípios ativos pode se estabelecer rapidamente após a introdução de novas moléculas, principalmente quando programas alternativos de controle não são realizados.

Palavras-chave: Ovinocultura, nematoides gastrintestinais, controle químico de parasitos, resistência.

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Introduction

In the first decade of the 21st century, Brazil reached the status of the 17th largest sheep producer in the world, with a flock of 17.3 million head (FAO, 2012). More than 3.9 million of these animals belonged to breeders in the state of Rio Grande do Sul (IBGE, 2012), a region where the activity is of great importance for the economy and provides subsistence for families from rural areas (SILVA et al., 2013). The economic expansion of sheep farming has also become a worldwide reality (VERÍSSIMO et al., 2012).

There are reports that, in the state of Rio Grande do Sul, parasitic diseases represent from 24.3% to 66.8% of the diagnoses performed in sheep flocks (RISSI et al., 2010). This includes gastrointestinal parasites, a major cause of mortality and reduced productivity in small ruminants (CHARLIER et al., 2014b). In the majority of properties, anthelmintics are still the main parasitic control tool (LARA, 2013) and indiscriminate use of anthelmintics has contributed to the selection and establishment of resistant parasites (ALMEIDA et al., 2010). This fact represents one of the greatest problems for the effective control of parasites in sheep (MOLENTO, 2004; VERÍSSIMO et al., 2012), preventing the sustainability of global sheep farming (COLES et al., 2006).

The recognition of anthelmintic resistance in flocks depends on monitoring the efficacy of the treatments (VERÍSSIMO et al., 2012). Rarely do sheep farmers suspect parasitic control failures until the onset of outbreaks with clinical signs and deaths. At that moment, however, there are already great economic losses and the propagation of parasites resistant to the active principles employed (CEZAR et al., 2010). With the purpose of monitoring anthelmintic resistance, the fecal egg count reduction test (FECRT) is recommended for convenience and low cost and is suitable for evaluating all anthelmintic groups (COLES et al., 2006).

Therefore, the objective of this work was to evaluate the efficacy of commercially available anthelmintics for the chemical control of gastrointestinal parasites of sheep in the southern region of Rio Grande do Sul, Brazil.

Methods

Flock selection

In the records of the Regional Diagnostic Laboratory, Faculty of Veterinary Medicine of the Federal University of Pelotas, rural farms in the southern region of Rio Grande do Sul with sheep breeding were consulted. After interviewing owners interested in cooperating, flocks that had not been dosed in the last 45 days were pre-selected. At the end, laboratory tests for egg counts per gram of feces (EPG) allowed the selection of 22 properties with mean EPG ≥ 300 for at least 80% of the evaluated animals, since all the tests were performed in duplicate.

Anthelminthic resistance detection

In vivo fecal egg count reduction tests (FECRT) were performed in the period from March to July 2016, prioritizing the recommendations of the World Association for the Advancement of Veterinary Parasitology (WAAVP), regarding the detection of anthelminthic resistance (COLES et al., 1992). Thus, in each property 10 animals were randomly distributed in seven groups and randomized the following treatments: abamectin 0.2 mg/kg (Avotan®, MSD Saúde Animal) body weight; albendazole 3.4 mg/kg (Endazol®, Hipra); closantel 10 mg/kg (Diantel®, Hipra); Levamisole 7.5 mg/kg (Ripercol L 150 F®, Fort Dodge); Monepantel 2.5 mg/kg (Zolvix®, Novartis); trichlorphon (TRI) 50 mg/kg (Neguvon®, Bayer) and control (no anthelmintic treatment).

Fecal samples were collected directly from the rectal ampulla of each individual 14 days after the experiment was set up (D14) for EPG using the modified Gordon and Whitlock technique (UENO & GUTIERREZ, 1983) with a sensitivity of 100 eggs.

The reduction percentage (PR) of the stool egg count was estimated by the following equation:

$$PR = 100 \cdot \left(1 - \overline{X}_t / \overline{X}_c\right) \quad (1)$$

where $\overline{X}_t$ is the arithmetic mean of the egg count for the treatment group t, and $\overline{X}_c$ is the arithmetic mean for the control group, both D14. Worms are called susceptible to the active principle when (i) the PR is greater than or equal to 95% and (ii) the lower limit of the 95% confidence interval is greater than or equal to 90%. If only one of these criteria is observed, the effectiveness of the anthelmintic is said to be suspected.

For each experimental group (treatment) in D14, fecal samples of all animals were combined in equal proportions for culture (UENO, 1995) in vitro and subsequent identification of the larvae (VAN WYK & MAYHEW, 2013). The EPG count of each individual was then adjusted to the proportion of the gastrointestinal nematode genera to estimate the specific efficacy of the active principles.

All the experimental procedures were approved by the Committee of Ethics and Animal Experimentation of UFPel (Protocol CEEA nº 7453-2015).

Results

The farms studied are between 18 and 6000 ha, with flocks consisting of 75 to 750 sheep. Eighteen farms used extensive breeding system and four semi-intensive breeding systems. The breed purposes varied among the 22 farms. In ten farms, sheep were raised for both meat and wool production, in seven farms for meat production, in three farms for breeding stock and meat and wool production, and in two farms for breeding stock and meat production.

Table 1 shows the percentages of reduction of fecal egg counts for each property, while the corresponding efficacy is summarized in Table 2. The specific action of the drugs against the genera of the parasites is also described in Table 3. Resistance to at least three anthelmintic agents was reported on all properties (Table 1). However, no sensitivity was reported for any of the active principles tested on two of these (11 and 22) properties. In addition, none of the other flocks (20/22) had more than two drug options to define an effective parasitic chemical control strategy.

Table 1. Reduction percentage (PR) of fecal egg count after 14 days of anthelmintic treatment in 22 sheep flocks in the Southern Brazil.

Flocks	Anthelminthic											
	CLO		MON		ALB		LEV		ABA		TRI	
1	87.1	(67.7)	100.0	-	90.3	(70.4)	93.5	(72.8)	87.1	(67.7)	67.7	(21.4)
2	84.4	(66.0)	100.0	-	90.6	(71.2)	93.8	(73.6)	93.8	(73.6)	78.1	(36.9)
3	87.1	(45.6)	100.0	-	90.3	(55.3)	87.1	(33.6)	100.0	-	74.2	(30.0)
4	75.5	(00.4)	100.0	-	73.6	(-58.6)	100.0	-	88.7	(68.5)	96.2	(82.2)
5	84.0	(60.1)	92.0	(66.4)	92.0	(66.4)	60.0	(25.2)	100.0	-	68.0	(-56.5)
6	96.3	(83.2)	96.3	(83.2)	85.2	(36.2)	72.2	(38.2)	92.6	(59.4)	100.0	-
7	51.1	(-20.9)	83.0	(44.6)	38.6	(-95.4)	65.9	(07.5)	79.5	(30.9)	98.9	(90.4)
8	91.0	(56.3)	100.0	-	67.2	(23.2)	98.5	(87.0)	76.1	(-01.3)	95.5	(85.2)
9	83.3	(58.6)	100.0	-	80.6	(51.4)	-22.2	(-186.6)	100.0	-	97.2	(76.0)
10	90.0	(68.3)	100.0	-	63.3	(23.2)	73.3	(36.0)	96.7	(71.5)	73.3	(30.4)
11	62.5	(-01.5)	91.7	(65.1)	54.2	(05.1)	75.0	(42.7)	87.5	(62.1)	87.5	(42.6)
12	84.4	(58.2)	100.0	-	31.3	(-76.7)	59.4	(18.0)	100.0	-	46.9	(-51.9)
13	85.7	(65.6)	100.0	-	89.3	(68.3)	92.9	(70.7)	85.7	(65.6)	85.7	(53.7)
14	87.0	(40.4)	100.0	-	52.2	(01.8)	97.8	(81.9)	65.2	(-37.2)	93.5	(80.3)
15	83.3	(65.4)	100.0	-	90.0	(70.3)	93.3	(72.5)	93.3	(72.5)	76.7	(34.8)
16	56.7	(-51.5)	100.0	-	53.3	(-150.0)	100.0	-	80.0	(55.1)	93.3	(72.4)
17	86.7	(67.2)	100.0	-	93.3	(72.2)	66.7	(38.7)	100.0	-	73.3	(-29.5)
18	76.9	(48.9)	100.0	-	84.6	(50.2)	42.3	(-15.2)	100.0	-	96.2	(68.3)
19	69.0	(18.6)	100.0	-	69.0	(39.5)	82.8	(55.2)	89.7	(69.4)	89.7	(53.4)
20	93.1	(71.6)	100.0	-	82.8	(64.3)	89.7	(53.3)	93.1	(71.6)	96.6	(71.5)
21	93.8	(74.3)	96.9	(74.2)	87.5	(59.4)	53.1	(15.1)	87.5	(37.1)	100.0	-
22	0.0	(-73.7)	90.0	(54.6)	73.3	(46.5)	76.7	(47.3)	83.3	(65.1)	96.7	(72.4)

Notes: 87.1 (67.7) —> reduction percentage (lower limit of the 95% confidence interval); - ("dash") —> unavailable due to the absence of variance for the OPG. Susceptible: PR is greater than or equal to 95% and the lower limit of the 95% confidence interval is greater than or equal to 90%. If only one of these criteria is observed, the effectiveness of the anthelmintic is said to be suspected. CLO: closantel 10mg/kg body weight; MON: monepantel 2.5mg/kg; ALB: albendazole 3.4mg/kg; LEV: levamisole 7.5mg/kg; ABA: abamectin 0.2mg/kg; TRI: trichlorphon 50mg/kg.

Table 2. Number of farms (% of total) found to be susceptible, resistant or suspected of resistance to the different anthelmintics used in a survey in 22 sheep flocks in Southern Brazil.

Efficacy	Anthelminthic												Total	
	CLO		MON		ALB		LEV		ABA		TRI			
Susceptible	0	(0.00)	16	(0.73)	0	(0.00)	2	(0.09)	6	(0.27)	3	(0.14)	27	(0.205)
Resistant	21	(0.95)	4	(0.18)	22	(1.00)	18	(0.82)	15	(0.68)	13	(0.59)	93	(0.705)
Suspected	1	(0.05)	2	(0.09)	0	(0.00)	2	(0.09)	1	(0.05)	6	(0.27)	12	(0.091)

Notes: 21 (0.95) —> Absolute frequency (adjusted relative frequency). CLO: closantel 10mg/kg body weight; MON: monepantel 2.5mg/kg; ALB: albendazole 3.4mg/kg; LEV: levamisole 7.5mg/kg; ABA: abamectin 0.2mg/kg; TRI: trichlorphon 50mg/kg.

Regardless of the active principle, in only 20.5% of the FECRT were the parasites susceptible to the anthelmintics tested (Table 2), excluding those suspected ones (9.1%). In 16 cases where the drug had effective action in parasite control, the animals were dosed with monepantel. In three farms where there was resistance to monepantel and this active principle had been used previously, the selective treatment, EPG and FECRT, were not applied. In another farm where there was no report of the previous use of this active principle and there was resistance to monepantel, the selective treatment (FAMACHA) was applied, EPG was performed every six months and FECRT every 12 months. Suspicion of resistance to monepantel was observed in two farms where the selective treatment, EPG and FECRT were not applied and also there was no report of previous use of this active principle.

Although some tests have also identified parasites susceptible to abamectin, levamisole and trichlorphon, flocks prevail with resistant parasites to these last three drugs. There is no doubt about this condition for those treated with albendazole.

Larvae of *Haemonchus*, *Oesophagostomum*, *Trichostrongylus* and *Teladorsagia* represented, on average, 41.1%, 31.8%, 18.7% and 8.3%, respectively, of the nematodes identified in the fecal cultures of the control groups. However, to estimate the specific efficacy of the active principles (Table 3), the presence of these larvae in each stool culture of the control group is necessary, a restriction imposed by the PR equation itself.

Thus, when comparing these results with nonspecific efficacy (Table 2), the data suggested that cases of drug-specific insensitivity are mainly due to the high prevalence of resistant strains of *Haemonchus* and *Trichostrongylus*, since these genera represented,

Table 3. Specific efficacy of anthelmintic submitted to the fecal egg count reduction test and fecal culture in 22 sheep flocks of the Southern Brazil.

Eficacy	***Haemonchus***												**Total**	
	CLO		**MON**		**ALB**		**LEV**		**ABA**		**TRI**			
Susceptible	0	(0.00)	21	(0.95)	1	(0.05)	5	(0.23)	7	(0.32)	4	(0.18)	38	(0.29)
Resistant	21	(0.95)	0	(0.00)	21	(0.95)	17	(0.77)	14	(0.64)	15	(0.68)	88	(0.67)
Suspected	1	(0.05)	1	(0.05)	0	(0.00)	0	(0.00)	1	(0.05)	3	(0.14)	6	(0.05)
Eficacy	***Oesophagostomum***												**Total**	
	CLO		**MON**		**ALB**		**LEV**		**ABA**		**TRI**			
Susceptible	9	(0.50)	18	(1.00)	17	(0.94)	17	(0.94)	18	(1.00)	8	(0.44)	87	(0.81)
Resistant	6	(0.33)	0	(0.00)	1	(0.06)	1	(0.06)	0	(0.00)	7	(0.39)	15	(0.14)
Suspected	3	(0.17)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.17)	6	(0.06)
Eficacy	***Trichostrongylus***												**Total**	
	CLO		**MON**		**ALB**		**LEV**		**ABA**		**TRI**			
Susceptible	3	(0.14)	20	(0.91)	4	(0.18)	5	(0.23)	9	(0.41)	6	(0.27)	47	(0.36)
Resistant	18	(0.82)	2	(0.09)	18	(0.82)	16	(0.73)	12	(0.55)	12	(0.55)	78	(0.59)
Suspected	1	(0.05)	0	(0.00)	0	(0.00)	1	(0.05)	1	(0.05)	4	(0.18)	7	(0.05)
Eficacy	***Teladorsagia***												**Total**	
	CLO		**MON**		**ALB**		**LEV**		**ABA**		**TRI**			
Susceptible	13	(0.93)	14	(1.00)	13	(0.93)	13	(0.93)	14	(1.00)	14	(1.00)	81	(0.96)
Resistance	1	(0.07)	0	(0.00)	1	(0.07)	1	(0.07)	0	(0.00)	0	(0.00)	3	(0.04)
Suspected	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)

Note: 21 (0.95) −> Absolute frequency (adjusted relative frequency). CLO: closantel 10mg/kg body weight; MON: monepantel 2.5mg/kg; ALB: albendazole 3.4mg/kg; LEV: levamisole 7.5mg/kg; ABA: abamectin 0.2mg/kg; TRI: trichlorphon 50mg/kg.

on average 59.9% of the flock parasitic load. In a few cases, strains of *Teladorsagia* were resistant to closantel, albendazole and levamisole. For the genus *Oesophagostomum*, there was a higher proportion of isolates insensitive to closantel and cases of resistance to trichlorphon.

Discussion

The results observed here demonstrate a worrying situation for sheep production in the southern region of the State of Rio Grande do Sul. Strong evidence suggests resistance of gastrointestinal parasites to the main commercially available anthelmintic agents, either by the criteria of Coles et al. (1992) or Brazilian legislation (BRASIL, 1997). This will become worse as none of the monitored properties have more than two drug options to define an effective chemical parasitic control strategy. There is no doubt that this scenario should also be a concern for other regions (GETACHEW et al., 2007; VÁRADY et al., 2011; CORNELIUS et al., 2014; FALZON et al., 2014), especially for those countries that border the state (Argentina and Uruguay).

Previous studies have also reported anthelmintic resistance in 97% of properties in Rio Grande do Sul. Albendazole resistance was reported on 90% of properties; levamisole resistance was reported on 84% of properties; and a combination of albendazole and levamisole resistance was reported on 73% of properties (ECHEVARRIA et al., 1996). In addition, the resistance to avermectins, benzimidazoles and imidazothiazoles is not uncommon in Brazil (ALMEIDA et al., 2010; FARIAS et al., 1997; WALLER et al., 1996). Other studies in Brazil have shown anthelmintic resistance to different active principles such as levamisole, moxidectin, albendazole, ivermectim, nitroxynil, disophenol, trichlorphon and closantel (CEZAR et al., 2010; SCZESNY-MORAES et al., 2010; ALMEIDA et al., 2010; VERÍSSIMO et al., 2012). Monepantel was not included in these studies since it was introduced in Brazil in 2012.

The animals in this study that did not receive anthelmintic treatment (control group) were not subjected to a pre-selection of their gastrointestinal parasites, which allows a better estimate of the corresponding population proportions of the nematode genera in the flocks. In contrast, the predominance of *Haemonchus* and *Trichostrongylus* is also frequently reported in studies conducted in Brazil (MELO et al., 2009; SCZESNY-MORAES et al., 2010; VERÍSSIMO et al., 2012). Particularly for the studied region, these parasites maintain a relatively homogeneous distribution throughout the year (ECHEVARRIA & PINHEIRO, 1989). This reinforces the concern about the contribution of these genera to the anthelmintic resistance status observed.

Monepantel, a derivative of aminoacetonitrile, is the most recent alternative in the chemical control of gastrointestinal parasites in sheep (HOSKING et al., 2010; KAMINSKY et al., 2011; SAGER et al., 2012). However, after three years of commercialization, it has already demonstrated resistant cases in New Zealand (SCOTT et al., 2013), Uruguay (MEDEROS et al., 2014) and the Netherlands (VAN DEN BROM et al., 2015). More recently, the first case of resistance was reported in Brazil (CINTRA et al., 2016). The results of the present study demonstrate that resistance to monepantel occurred mainly in the farms that did not take any action aiming at delaying the resistance. However, the resistance also occurred in a farm that performed alternative strategies for parasitic control such as selective treatment

(FAMACHA), EPG and FECRT. In this case resistance probably was established from purchased sheep previously infected by resistant parasites. It has been mentioned that alternative strategies are required to delay the onset of anthelmintic resistance to active principles (FORTES & MOLENTO, 2013).

Since the identification of new molecules does not accompany the unrestrained expansion of the cases of resistance, the means of dissemination of the scientific community and the development agencies should encourage publications that suggest good or innovative management practices to effectively control parasitic gastroenteritis in sheep.

Information on the biological cycle of helminths and climatic and economic conditions of each region should be considered when establishing parasitic control strategies. The use of ocular mucosa color (FAMACHA), parasite load on fecal examination, and weight gain of animals (COSTA et al., 2011; CHARLIER et al., 2014a) may also help to identify the best time for a chemical intervention. Other options include integrated management practices with the intention of minimizing the effects of parasitic infection through strategic and selective treatment schemes (HAMMERSCHMIDT et al., 2012). However, these technologies need to be encouraged more for wider acceptance among animal health producers and practitioners, which would avoid the indiscriminate use of ineffective drugs.

Conclusion

The results of this study provide evidence that the common commercially available anthelmintics are not assuring effective chemical control of gastrointestinal parasitic infections in ovine flocks in the southern region of Rio Grande do Sul. Monepantel the anthelmintic drug introduced in the Brazilian market was not effective in 18% of the tested flocks, confirming that parasitic resistance can be established very soon after the anthelmintic treatment with new molecules, mainly when alternative program of parasite control is not performed.

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