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Anthelmintic Resistance of Gastrointestinal Parasites in Small Ruminants: A Review of the Case of Ethiopia

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Abstract

Analysis of 13 published anthelmintic sensitivity studies against gastro-intestinal (GI) nematodes of small ruminants was conducted to describe anthelmintic use trends and resistance problems in Ethiopia. Anthelmentic use surveys in 5 small ruminant rearing areas indicated widespread risky practices including; marketing of unknown formulation drugs, professionally unsupervised prescription and use of drugs, inappropriate calculation of drug doses and exhaustive use of few drugs. Evidence of small ruminant GI nematode resistance to albendazole, levamisole, teramisole and ivermectin was aparent in 15 (32.9%), 5 (41.7%), 4 (25%) and 2 (13.3%) trials, respectively. Resistance to multiple antihelmintic families was recorded in 4 studies conducted at 2 experimental goat farms. The nematode populations implicated in resistance belonged to *Haemonchus, Oesophagostomun, Trichostrongylus* and *Trichuris* species. Small ruminant GI nematode resistance to the broad spectrum anthelmintics is a significant livelihood and economic threat in Ethiopia. Strategic effort aimed at halting the emergence and spread of anthelmintic resistance is urgently needed.

Keywords: Anthelmintic; Goats; Nematodes; Sheep; Sensitivity

Introduction

Ethiopia is home to some 23.62 million sheep and 23.33 million goats [1]. Estimates indicate that small ruminants account for 35% of the meat and 14% of the milk consumption, as well as the biggest share of hide and skin export earnings in Ethiopia [2]. However, the productivity of small ruminants in the country is limited by; widespread health problems, poor feeding and husbandry practices, and low technological support [1,3]. Gastrointestinal (GI) parasites are one of the principal health problems reducing the productivity of small ruminants. Numerous studies had confirmed a widespread prevalence of GI helminthic infestation in all small ruminant rearing regions in Ethiopia [4-6].

Effective management of GI parasites in grazing livestock relies on the strategic use of highly efficacious chemotherapy [7]. However, decades of indiscriminate use has resulted in widespread development of anthelminthic resistance (AR) including multi-drug resistance in various GI nematode populations [8]. AR is the situation where normal dosage of a drug does not produce a consistent reduction in worms or excreted eggs [9]. Failure to identify AR and manage its development will incur severe production penalties due to the impact of parasitic gastroenteritis [7]. Considering the narrow range of available drugs and slow rate of new drug development, AR presents an alarming global threat demanding vigilant monitoring and management.

The use of anthelmintics has been practiced for a long time and constitutes a major share of the veterinary service costs in Ethiopia [10]. Broad spectrum antihelmintics commonly used for management of livestock GI helmenthic infestation in Ethiopia fall under three families, including; Bezimidazoles (Albendazole and Triclabendazole), Imidazothiazoles (Tetramisole and Levamisole) and Macrocyclic Lactones (Ivermectin). Decades of unregulated and unsystematic antihelmentic use has failed to abate livestock GI parasitism, but instead, led to emergence of AR in different nematode populations under different agro-ecological zones in Ethiopia [11-16].

This technical analysis was conducted with an aim of summarizing published antihelmintic use and sensitivity study reports pertaining to GI nematodes of sheep and goats in Ethiopia. The analysis attempted to evaluate shortfalls in current anthelmintic use trends and to describe the distribution of anthelmintic resistance to commonly used drug families.

Methods

A total of 13 studies reporting 5 anthelmintic use surveys and 50 anthelmintic sensitivity trials pertaining to small ruminant GI nematodes were analyzed for this technical review. The studies covered all major small ruminant rearing regions of Ethiopia. Experimental trials covered 31 distinct geographic locations including experimental farm (12) and small holder farm (38) settings. Except for 3 trials on experimentally infected lambs, remaining anthelmintic sensitivity studies were conducted in naturally infected sheep (27) and goats (20).

Analysis of GI nematode sensitivity studies was focused on three families of anthelmintic commonly circulating in Ethiopian markets. As such sensitivity to benzimidazoles (albendazole), imidazothiazoles (tetramisole and levamisole) and marcocylic lactones (ivermectin) was tested in 43, 32 and 15 trials, respectively. The experimental doses of drugs used was variable for albendazole (7.5, 5 and 3.5 mg/kg), tetramisole (22.5 and 15 mg.kg) and ivermectin (0.2, 0.22 and 0.3 mg/kg) but uniform for levamisole (7.5 mg/kg). The origin of experimental drugs ranged from African (Ethiopia and SA), Asian (Chinese, Indian, Pakistani and Korean) or Western (USA, UK, Ireland, Greece).

Antihelmintic sensitivity of GI nematodes was reported as fecal egg count reduction (FECR)% mean in 13 (100%) and as 95% CI's in 8 (61.5) studies. FECR was reported at 10th, 12th, 14th or 10-14th day post

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treatment in 5, 4, 2 and 2 studies, respectively. Post-treatment fecal culture and nematode larvae identification results were available for 6 (46.15%) studies.

Descriptive statistics were used to summarize antihelmintic use and resistance findings. Anthelmintic resistance was independently defined as per the World Association for the Advancement of Veterinary Parasitology (WAAVP) recommended criteria's i.e. mean post-treatment FECR less than 95% and/or lower limit of FECR 95% CI less than 90% [17].

Results

Anthelmintic use

Anthelmentic use practice of small ruminant farmers was surveyed in central, eastern, western, southern and northern Ethiopia. Seasonal deworming was reported only in northern Ethiopia. In the remaining study areas, farmers administer anthelmintics only when animals present signs of illness (digestive, respiratory and related). Anthelmintic was usually selected based on criteria's other than veterinary advice (low price, color, size, ease of use, etc). Purchase of drugs from professionally unsupervised sources (open-markets and illegal distributors) was also a common practice (Table 1). Farmers administered anthelmintics themselves and dosage was always determined according to estimated body weight. Meanwhile, strategic rotation between antihelmintic families was virtually absent in all regions surveyed.

Antihelmintic resistance

Evidence of small ruminant GI nematode resistance to commonly used anthelmintics was evident in 26 (52%) trials. Resistance was detected in all 4 corners and central parts of Ethiopia against; albendazole 15/43 (32.9%), levamisole 5/12 (41.7%), tetramisole 4/20 (25%) and ivermectin 2/15 (13.3%). Anthelmintic resistance was more frequent in goat 17 (65.4%) than sheep 9 (34.6%) nematodes. The small ruminant GI nematode populations implicated in resistance belonged to *Haemonchus, Oesophagostomun, Trichostrongylus* and *Trichuris* species (Table 2). Resistance to both benzimidazoles and imidazothiazoles was detected on 2 studies in *Hemonchus* and *Trichuris* spp. Moreover, *Heamonchus* and *Trichostrongylus* spp. demonstrated resistance to all three broad spectrum anthelmintic families in 2 studies. All cases of multiple drug resistance were observed in goats kept under experimental farm setting (Table 2).

Six (40%) albendazole and 3 (60%) levamisole resistance cases had mean FECR ≥ 95% but FECR 95% CI lower limit <90%. Resistance to albendazole was detected more frequently under experimental dosage of 5 mg/kg 8 (53.3%) followed by 7.5 mg/kg 5 (33.3%0 and 3.5 mg/kg 2 (13.3%). The origin of experimental albendazole implicated with resistance was unknown (4), Indian (3), Ethiopian (2), Greece (1) or Chinese (1). Experimental tertamisole implicated in resistance originated from Greece (2), SA (1) and India (1). Both experimental doses of 22.5 mg/kg (3) and 15 mg/kg (1) were implicated in resistance. Origin of experimental levamisole implicated with resistance was unknown (4) and Indian (1). Meanwhile, experimental ivermectin (02 mg/kg) associated with resistance originated from Ireland and unknown source.

Discussion

GI parasitic infections are a major constraint in grazing livestock particularly in tropical and sub-tropical regions [4,24,25]. Veterinary control interventions attempt to ensure that parasite populations do not exceed levels compatible with economic production. This objective could be achieved by three main approaches: grazing management, use of anthelmintics, and utilization of natural or artificially induced immunity [24]. Owing to their high efficacy and ease of use anthelmintics represent a cornerstone for GI nematode control programs. Three broad spectrum anthelmintic families are commonly used to control GI nematodes of small ruminants: benzimidazoles, imidazothiazoles and macrocyclic lactones [9].

Safe and effective use of antihelminthics requires professional regulation and supervision. The Ethiopian "Veterinary Drug and Feed Administration and Control Proclamation No. 728/2011", stipulates that all veterinary drugs shall only be prescribed by a veterinarian in strict adherence to standard guidelines. Meanwhile, analysis of anthelinitic use surveys in different small ruminant rearing regions of Ethiopia indicate widespread infringements including; marketing of unknown formulation drugs, professionally unsupervised prescription and use of drugs, inappropriate calculation of drug doses and exhaustive use of few drugs. Hussein et al. [26] and Kumsa and Wesene [27] also observed widespread misuse and smuggling of anthelmintics as well as lack of a rational policy for anthelmintic use in Ethiopia. Frequent and/or long term use of one anthelmintic is a way to efficiently select a sub-population of worms that develop capacity to survive the particular drug [9]. Under-dosing, attributed to poor drug formulation or animal weigh miss estimation, facilitates the buildup of resistance against an anthelmintic [28].

The future of the broad spectrum anthelmintic families has come under threat due to emergence of resistance in different parasitic populations. AR in gastrointestinal nematodes of sheep and goats has been reported from different parts of the world [29] including countries like Kenya and South Africa [30]. Scientific information on GI parasites AR problems prevailing under small holder farm settings is limited in Ethiopia. Analyses of accessible published study reports indicate wider distribution of resistance to benzimidazoles as well as evidence of resistance to imidazothiazoles and macrocyclic lactones in Ethiopia. This is probably a reflection of market circulation and use trend of the anthelmintic families. Albendazole, a benzimidazole, is the most widely used anthelmintic in Ethiopia [6]. Resistance to multiple (2 and

	AH source		AH selection		
Study area	**Veterinary**	**Non-veterinary**	**Veterinary advice**	**Other criteria**	**Source**
Zeway - CE	33	67	5	95	[18]
Bedele - WE	90	10	50	50	[19]
Fafen - EE	NR	NR	20.9	79.1	[6]
Hawasa - SE	47%	53	10	90	[20]
Gondar - NE	55.6	44.4	NR	NR	[21]
Average	**56.4**	**43.6**	**21.5**	**78.5**	

NR - Non Reported; CE, NE, SE, EE and WE: Central, Northern, Southern, Eastern and Western Ethiopia.

Table 1: Summary of Anthelmintic (AH) sources and selection criteria (%).

Antihelminthic	Locality	Host	Nematodes population involved	Source
Albendazole (43 trials)	Shashemene - CE	Goat	*Haemonchus spp*	[15]
	Mojo - CE	Sheep		
	Chacha - CE	Sheep		
	Sheno - CE	Sheep		
	Haramaya university - EEc (3) a	Goat		
	DSBIC - CE	Sheep		
	Zeway goats - CE [b]	Goat	*Trichuris spp*	[18]
	Sidama - WE	Sheep		[16]
	Sidama - WE	Goat		
	Hawasa - SE (2)	Sheep	*Heamonchus spp*	[20]
	Hawasa University - SE[c]	Goat	*Haemonchus, Oesophagostomun and Trichostrongylus*	[22]
	Haramaya university - EE[d]	Goat	*Haemonchus spp*	[23]
Tetramisole (20 trials)	Ziway goats - CE [b]	Goat	*Nematodes & Trichuris*	[18]
	Gondar - NE	Sheep	*Trichuris, Haemonchus, Oesophagostomun*	[21]
	Hawasa University - SE [c]	Goat	*Haemonchus, Oesophagostomun and Trichostrongylus*	[22]
	Haramaya university - EE [d]	Goat	*Haemonchus spp.*	[23]
SLevamisole (12 trials)	Zeway - CE	Goat	*Haemonchus spp*	[18]
	Haramaya university - EE (3) [a]	Goat	*Haemonchus spp*	[15]
	Gondar - NE	Sheep	*Trichuris, Haemonchus, Oesophagostomun spp.*	[21]
Ivermectin (15 trials)	Hawasa University - SE [c]	Goat	*Heamonchus and trichostrongylus spp.*	[22]
	Haramaya university - EE [d]	Goat	*Haemonchus spp*	[23]

Superscripts a-d represent instances of multiple drug resistance, numbers in bracket indicate number of trials DSBIC: Debre Berhan Sheep Breed Inmprovment Center; CE, NE, SE, EE and WE: Centeral, Norther, Southern, Eastern and Western Ethiopia

Table 2: Distribution of antihelmintic resistance in GI nematodes of small ruminants in Ethiopia.

3) broad spectrum anthelmintic families was observed in *Haemonchus, Trichuris* and *Trichostrongylus* spp. from goats under experimental farms settings. Frequency of multi-drug resistance in experimental farm settings could be a reflection on the more intensive use and rotation of anthelmintics also suggested by Sissay et al. [23]. Therefore, distribution of improved breeding stalk from experimental stations to small holder farms could pave way for the spread of multidrug resistance involving recognized parasitic causes gastroenteritis. Such spread of multi-drug resistance threatens sustainability of anthelmintic control of farm animal parasitic infestations. Efforts to break emergence and spread of anthelmintic resistance are urgently needed in Ethiopia. Strategic rotation between anthelmintics can reduce selection pressure against resistance to individual drug families [9]. Combinations of anthelmintics from different families for treatment could provide an effective strategy for eliminating multi-drug resistance in problem herds [31].

Conclusion

Small ruminant GI nematode resistance against the three families of broad spectrum anthelmintics is evident in Ethiopia. The distribution pattern of anthelmintics resistance reflects intensity of use for concerned antihelmintic families. Frequent use and rotation of anthelmintics tend to increase risk of multiple antihelmintic resistance in experimental farm settings. Meanwhile, small ruminant GI nematode resistance appears restricted to single anthelmintic families and attributed to overuse and misuse of drugs under small holder farms. Poor regulation of drug marketing and professionally unsupervised drug use increase risk of athelmintic resistance development in Ethiopia. Measures that ensure the quality of drugs entering markets need to be improved. Strategic use of anthelmintics is badly needed to; enhance impact of control interventions, reduce selection pressure on antihelmintics resistance and eliminate resistant nematode populations.

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