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An overview on Anthelmintic drug resistance against gastro-intestinal nematodes of ruminants with particular emphasis to Ethiopian situation

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Abstract

The control of parasitic nematodesin domestic ruminants over the past many years and eventoday is mainly based on the use of chemotherapeutics. However, by way of their inheritable genetic behaviour, GI nematodes have consistently found ways to evadethe existing control measures. As a result, the globe currently faced with an ever increasing spread of anthelmintic resistance (AR) and infection patterns that may be altered by a changing climate, changes in land-use and associated farm husbandry alteration. Anthelmintic resistance has grown in several animal industries and is currently believed to threaten the control of human parasitesand animal parasites. Resistance is probably an inevitable consequence of the improper use of anthelmintic. In most regions of Africa, the development of anthelmintic resistance could be expected to be slow, because of highrefugia and low frequency of treatment. The exception is South Africa, where in large-scale commercial sheep farms the intensive and frequent use of anthelminticshas led to very high levels of multiple anthelmintic resistances. However, the overall prevalence of anthelmintic resistance has not been extensively investigated throughout the African continent; anthelmintic resistance in sheep and goat parasites has been reported from several countries.The occurrence of anthelmintic resistance to commonly used drugs is becoming worldwide problem in livestock production. Considering the narrow range of available drugs and slow rate of new drug development, anthelmintic resistance presents an alarming global threat demands vigilant monitoring and management. The anthelmintic resistance against gastrointestinal nematodes is likely to be present in Ethiopian situation.

Keywords: Anthelmintic resistance, Domestic ruminants, Nematodes

Introduction

Gastrointestinal (GI) nematodes are worldwide problem which reduces production of livestock in many countries. The impact is greater in sub-Saharan Africa including in Ethiopia due to the availability of a wide range of agro-ecological factors suitable for diversified host and parasite species (Hammond et al., 1997; Regassa et al., 2006). The severity of helminthes parasites vary considerably depending on prevalence, genera, species involved and local environmental, such as humidity, temperature and rainfall (Anderson et al., 1993). Several scholars confirmed a widespread prevalence of small ruminant nematodes in different parts of Ethiopia. For example, 69.01% of small ruminants harbor one or more genera of nematodes (Dilgasa et al., 2015). Study in eastern part of Ethiopia stated the prevalence of nematodes in sheep and goats with *Haemonchus contortus* being the most prevalent followed by Trichostrongylus spp (Sisay et al., 2007). Other study in south west Ethiopia Kaffa reported that 54.1 % of small ruminants were positive for GI parasites eggs (Tigist et al., 2015). Resistance of GI parasites to currently available anthelmintics has been

occurred worldwide. Different researchers confirmed the occurrence of anthelmintic resistance (AR) to commonly used drugs and the problem associated with development of anthelmintic resistant parasites is becoming a major worldwide constrain in livestock production and hence need to detect and monitor resistance nematodes (Wolstenholme et al., 2004; Kaplan et al., 2004; Makvana and Veer, 2009).

The aim of this review was to bring together available data from primary research conducted so far on Anthelmintic drug resistance against gastro-intestinal nematodes of ruminants with particular emphasis to Ethiopian situation and to indicate the current situation and preventive approached.

Anthelmintic drug resistance situation in Ethiopia

Gastrointestinal helminth infections are very common in many parts of Ethiopia and their control is mainly based on anthelmintic treatment (Fikru et al., 2006). Aberra (1992) reported the coproscopic prevalence of helminth parasites in Bedelle district of Western Oromiato be around 90%.Anthelmintic drug resistance is a growing problem in the country. Some of the common causes that contribute to the development of anthelmintic resistance are unnecessary use of anthelmintic drugs, inappropriate dose, inadequate duration of therapy, use of irrational drug combinations(Kassahun et al., 2016).

The extensive use of anthelmintics for the control of helminth infections on grazing livestock has resulted in the development of resistance that has become a major practical problem in many countries of Africa (Waruiru, (1997); Van Wyk *et al.,* 1997). A similar situation has been reported in eastern Ethiopia by Sissay et al (2006) where nematodes have shown resistance to albendazole, tertramisole and ivermectin at prescribed dosages in small ruminants. On the other hand, an experimental study on *Heamonchus contortus* infection in sheep has shown 100% efficacy of ivermectin (Yacob et al., 2008). Highly prolific species such as *H. contortus* with relatively short life expectancy of adult worms have a higher risk of developing diverse resistance-alleles due to spontaneous mutations than the less prolific *T. colubriformis* (Silvestre et al., 2002).

Their long-term utilization, inappropriate handling and under dosage may be some of the reasons for their reduced efficacy and for the increasing development of drug resistance. A study done on the blood feeding parasite, *H. contortus* has demonstrated the existence of multiple-resistance to repeated applications of benzimidazoles, levamisole and ivermectin (Waruiru, (1997). Since anthelmintics within each drug class act in a similar manner, resistance to one anthelmintic in a given drug class is likely to be accompanied by resistance to other anthelmintics of that same class (side resistance). There is also the likelihood for the development of cross resistance from anthelmintics of one drug class to those of another, if the two drug classes share similar targets. Hence, the widespread occurrence of resistance across the majority of anthelmintic drug classes (Sisay et al., 2006).

Anthelmintic resistance has increased to become an important economic problem in several animal industries. The modern broad-spectrum anthelmintics are currently widely used in prophylaxis and treatment of helminth infections in farm animals. The problem of resistance to chemotherapeutic drugs has gradually grown from its rather sporadic occurrence in the early 1960s to the current status where anthelmintic resistance threatens the sustainability of many intensive systems of production(Várady et al.,2011).

Table 1. Major reported resistances to commonly used anthelmintics in Ethiopia

		Broad spectrum					Specific group/Narrow spectrum						
		Izs		Ms			Snl						
Host	Helminth parasite	Bzs	M/P	Lev	Ivm	Mxd	Dmt	Mbc	Cst	Rxn	Opp	Oxa	Ppz
Sheep	Trichostrong.spp.	+		+	+	+			+	+			+
	H. contortus	+	+	+	+	+				+	+		
	Trichurisspp.	+		+	+	+			+	+			
	O.ostertagi												
	Cooperiaspp.												
	F.hepatica	+								+			
Goat	Trichostrongspp.	+		+									
	H. contortus	+	+	+	+					+			+
	O.ostertagi	+											
Cattle	Trichostrong. spp.	+											
	H. contortus	+		+	+	+	+						
	Oesophagspp.								+				
	Trichurisspp.	+			+				+				
	O.ostertagi	+							+				
	Cooperiaspp.	+			+	+	+		+				
	F.hepatica												

Source: Nega and Seyoum (2018).

Bzs = benzimidazoles; Izs = imidazothiazoles [M = morantel, P = pyrantel]; Mls = macrocyclic lactones [Ivm = ivermectin, Mxd = moxidectin, Drm = doramectin]; Sns = salicylanilide [Mbc = milbemycin; Cst = closantel]; Rxn = rafoxanide; Opp = organophosphate; Oxa = oxamniquine; Ppz = piperazin.

Mechanisms of anthelmintic resistance

Anthelmintic Resistance mechanisms includes mutation or deletion of one or more amino acids in the target genes, reduction in the number of receptors, decreased affinity of receptors for drugs, and absence of bioactivating enzymes. Due to modern molecular technology, mechanisms of resistance in worms are becoming further understood. Resistance in worms can be the result of a variety of mechanisms and can be categorized as genetic changes in the drug target, in the drug transport or in the drug metabolism. The cause of resistance in worms is often complex. Whereas nematode resistance to benzimidazoles can be due to a mutation in the gene coding for the target site, the same mutation(Furgasa *et al*.,2018).

There are several phases in the process of resistance development. Firstly, there is an initial phase of susceptibility where the number of resistant individuals within the parasite population is low with continued exposure to the same drug group. An intermediate phase then follows in which the frequency of heterozygous resistant individuals within the population increases. Finally, sustained selection results in a resistant phase where homozygous resistant individuals predominate within the population. The speed of this process will depend on how severe selection pressure is on the parasite population. It is known that this is linked to the frequency of treatment and the fact that widespread and excessive use (8 to 12 times per year) of the drugs without considering the ecology of the parasites, has led to the development of resistance of the parasites to drugs (Verma et al., 2018) .

Analysis of resistance mechanisms in several organisms is warranted as their general biochemical framework of resistance is often similar. Cells may evade drug action by hiding in sanctuaries; drug uptake may be thwarted by loss of uptake systems or alteration of membrane composition; once inside, drugs may be inactivated, excreted, modified and excreted, or routed into vacuoles; drug activation mechanisms may be suppressed or lost; the interaction of drug with target may be made less effective by increasing the level of competing substrates or by altering the target to make it less sensitive to the drug; the cell may learn to live with a blocked target by passing the block (Ouellette, 2001) .

Table 2. Anthelmintic family and mechanism of resistance

Anthelminthic family	Mechanisms of resistance	Comment
Benzimidazoles	B-tubulinisotype 1 mutations: f200y, f167y,	The best studied mutations and probably the most important.
	B-tubulinisotype 2 mutations: f200y, f167y, deletion.	F200y seems to be the most important mutation in *haemonchuscontortus*, but this might not be true for all species.
Avermectins and milbemycins	Mutations in glucl and/or gaba-r genes	Molecular evidence from *cooperiaoncophora*:genetic evidence from *H. contortus*.
	Overexpression of p-glycoproteins population	Population genetic and some pharmacological evidence. The relative importance of these two mechanisms is yet to be determined.
Levamisole	Changes in nicotinic	Physiological and pharmacological evidence: no molecular data to date.

Source: Nega and Seyuom(2017)

The general consensus is that anthelmintic resistance appears to be a pre-adaptive heritable phenomenon with the gene or genes conferring resistance being present within the parasite population even prior to the drug being used for the first time. Under these circumstances resistance arises as a result of selection through exposure of the worm population to an anthelmintic. When an animal is optimally exposed to an anthelmintic the only worms that should survive are those that carry the genes that confer resistance. For a short period (until the animal becomes re-infected with drug susceptible worms from pasture) the resistant survivors are the only worms laying eggs and in this way the gene pool for resistance is increased. The rate of development of resistance is influenced by many factors, of them, significant ones are described here(Hatam et al.,2013).

Detection of anthelmintic drug resistance

Different methods have been described to detect a presence of resistance to anthelmintic. These methods can be divided in to *in-vivo* (Fecal egg count reduction test, worm burden reduction test)and *in-vitro* (egg hatch assay, larval paralysis assay, larval migration inhibition assay etc...)techniques. The *in-vivo* methodsare suitable for all types of anthelmintic, including those that undergo metabolism in the host to chemically active compounds. In vitro techniques offer rapid, sensitive and considerably more economic methods of screening but suffer from certain limitations(Furgasa et al.,2018).

Faecal Egg Count Reduction Test (FECRT): This is the most common test to study anthelmintic resistance. The ability of the anthelmintic in question to reduce the concentration of eggs per gram of faeces (EPG) by more than 95%, measured 10-14 days after treatment, in comparison with the EPG measured at the time of treatment. Failure to do so is indicative of resistance. This test was originally designed for sheep, but can be used also for cattle, swine and horses. Cut-off value for drug efficacy in FECRT 95% and 90%, macrolides and benzimidazoles / pyrantel, respectively(Verma *et al.*, 2018). For The worm reduction test, animals are necropsied at the end of the trial, after which the remaining worms in the intestinal tract of the treated animals are compared with those from animals that did not receive any treatment (Rinaldi et al., 2014) . Controlled test is considered the gold standard in measuring efficacy of anthelmintics ,which is the most reliable method of assessing anthelmintic efficacy against mixed nematode infections. These tests the efficacy of an anthelmintic by comparing parasite populations in groups of treated and recommended untreated animals. Basically, the procedure compares worm burdens of animals artificially infected with suspected resistant isolates of nematodes. The parasitized animals are randomly separated into medicated and non-medicated groups and the animals are necropsied after treatment interval (10 to 15 days) and the parasites are recovered to be identified and counted. This test must be compulsorily done before the registration of a new drug and is not extensively used except in cases of special interest or when confirmation of resistance is required at species level and for evaluation of the effect on larval stages (Yitayew *et al*., 2016).

Several different *in-vitro* tests are available but the majority is almost exclusively used for research purposes. These tests can be used to quantify the level of resistance but they require considerable technical expertise and in some cases, expensive laboratory equipment. Ideally, these tests require mono-specific infections. The maintenance of standard laboratory strains, both drug susceptible and resistant is necessary for comparative purposes. The main in vitro bioassays are listed in Table 3(Nega et al., 2018) .

Table 3. Bioassays for the diagnosis of anthelmintic resistance

List of Assays	Application
Egg hatch Assay	Benzimidazoles/levamisole/morantel
Larval paralysis	Levamisole/morantel
Tubulin binding	Benzimidazoles
Larval development	All drugs
Adult development	Benzimidazoles

Sourc: Nega et al(2018)

The egg hatch assay has been developed to differentiate between resistant and susceptible strains of gastrointestinal nematodes for the BZs and for the levamisoles that used to calculate the 50% of lethal dose of the drug on freshly collected nematodes eggs. It provides an accurate method for assessing the susceptibility of mixed nematode populations and comparatively more rapid and economic to conduct than the FECRT(Demessie et al., 2016) .The principle is based on determination of the proportion of the eggs that fail to hatch in solution of increasing drug concentration in relation to the control wells enabling the user of the test to develop a dose response line plotted against the drug concentration(Nega et al.,2018). The long term stability of thiabendazole in solutions of DMSO is not known but reduction in anticipated concentrations may occur when stock solutions are diluted in water(Coles et al., 2006).

To obtain meaningful data, eggs for the egg hatch test must be fresh and should be used within three hours of being shed from the host as sensitivity to some BZs decreases parasites, as embryonation proceeds. The test has only been shown to work on nematode species in which eggs hatch rapidly. There are several variations of the egg hatch assay, but the essential aim is to incubate undeveloped eggs in serial concentrations of the anthelmintic(Yitayew *et al*., 2016).

The larval paralysis and motility assay depends on the principle that estimates the proportion of the third stage larvae in tonic paralysis after incubation with a range of levamisole drug concentrations to differentiate between resistance and susceptible strain of parasites. It is relatively easy to carry out, fairly good reproducibility of test (Nega et al., 2018).

The larval development assay (LDA) is based on culturing a known number of GIN eggs in the presence of different anthelmintics. It is reported be relatively easy to perform, more sensitive than the FECRT and allows for the identification of parasite larvae to the genus level. LDA is the only one that allows to the detection of resistance against all the drugs irrespective of their mode of action. In this test, nematode eggs isolated from fecal samples are applied to the wells of a micro-titer plate and larvae hatch and develop to the L3 stage in the presence of anthelmintic. The concentration of anthelmintic required to block development is related to an anticipated in vivo efficacy (Yitayew *et al*., 2016).

The adult development assay is used for detecting benzimidazole resistance in trichostrongylid nematodes has advanced significantly and (Nega et al., 2018), (Verma et al.,2018) and *H. contortus* has been cultured through to the adult egg-laying stages, although this test is mainly for research purposes (Yitayew *et al*., 2016).

The most common molecular mechanism that confers benzimidazole resistance in trichostrongyles in small ruminants involves a phenylalanine to tyrosine mutation at residue 200 of the isotype 1 β-tubulin gene. However, in addition a similar mutation at codon 167 may be involved in benzimidazole resistance in nematodes. An allele-specific polymerase chain reaction (AS-PCR) has been used to detect this mutation in *H. contortus* and *Teladorsagia circumcincta* adult and larval stage(Verma et al.,2018). The key issue is that only when a diagnosis based on using pooled larval DNA samples can be obtained will it be possible to bring molecular resistant testing to routine use. Testing of representative numbers of single stages is prohibitively expensive. Also the available molecular tests mainly address resistance in species where the problem is widespread and in some cases may be too common to justify testing. The most common molecular mechanism that confers BZ resistance in trichostrongyles in small ruminants involves a phenylalanine to tyrosine mutation at residue 200 of the isotype 1 b-tubulin gene(Coles et al.,2006).

Management of anthelmintic drug resistance

The key areas of concern in the management of anthelmintic resistant throughout the world are: A) Drug related factors (pharmacokinetics, formulation and mode of application of anthelmintics). B) Management related factors (incorrect dosing of anthelmintics, frequency of anthelmintic treatment, and use of the same anthelmintic class for several years, pasture management of livestock). C) Parasite related factors (number of nematodes in refugia, frequency of genes for resistance in an unselected parasite population, genetic factors as mode of inheritance, fitness and fecundity of resistant nematodes, generation time(Verma *et al*., 2018).Considering the increasing concern regarding the development of drug resistance, the use of pharmacology-based information is critical to design successful strategies for future helminth parasite control in livestock. Integrated pharmacokinetic/pharmacodynamic and clinical pharmacology knowledge is required to preserve both well-established and modern anthelmintics. Assessment of drug disposition in the host and comprehension of the mechanisms of drug influx/efflux/detoxification in different target helminths, have signified relevant progress in anthelmintic therapy in ruminants. Moreover, different pharmacokinetic-based approaches to enhance parasite exposure (pharmacokinetic optimization) and the use of a mixture of molecules from different chemical families (drug combinations) have been assessed as valid strategies to control resistant parasites and to slow the selection for further resistance (Lanusse et al., 2018).

Alternatives to the use of chemical compounds such as grazing management, improving resistance of the parasites through selective breeding, by vaccination and provision of good nutrition are also of paramount importance. Control of pasture can reduce the impact of worm infection in livestock. Another approach is through the use of the pasture for different animals at different times such as bringing equine or cattle to the pasture for one season and using the pasture for sheep grazing in the next season. The reason is that sheep and cattle or equines do not share much of the important helminth parasites such as *Haemonchuscontortus*. However, implementation of this method needs a good knowledge about the

epidemiology of the helminth parasites that are endemic to that area, such as the knowledge about the time at which the helminth eggs are hatched and the larval populations reach the infective stage (Verma *et al.*,2018)

The most promising vaccine for small ruminant worms is based on a ‘‘hidden gut’’ antigen and specifically targets H contortus. This antigen is derived from the gut of the worm and, when administered to the animal, antibodies are produced. When the worm ingests blood during feeding, it also ingests these antibodies. The antibodies then attack the target gut cells of the worm and disrupt the worm’s ability to process the nutrients necessary to maintain proper growth and maintenance, thus killing the worms. This vaccine has been tested successfully only in sheep under experimental conditions and has had limited success under field conditions(Dyary, (2016)). On the other hand, reducing hosts exposure to infection through biological control on pasture such as by using nematophagus or nematode trapping fungi has also shown great promise. Research with nematode-trapping fungi has documented the potential as a biological control agent against the free-living stages under experimental and natural conditions. These fungi occur in the soil/ rhizosphere throughout the world where they feed on a variety of free-living soil nematodes. These fungi capture nematodes by producing sticky, sophisticated traps on their growing hyphae. Of the various fungi tested, Duddingtoniaflagrans, has the greatest potential for survival in the gastrointestinal tract of ruminants(Besier and Love, 2003).

The need to provide refugia through modification of worm control programs depends largely upon the environment and importance of local factors in drench resistance. Where environmental conditions promote the continual survival of worm larvae on pasture, a substantial pool of larvae in refugia (not exposed to drenches) is usually available on the livestock property involved. This presumably explains the relatively lower levels of anthelmintic resistance in non-*Haemonchus* species in temperate countries. However, where the treatment interval is close to the pre-patent period of the nematode species involved, non-resistant worms do not have an opportunity to contribute to the population, and resistance can develop rapidly. This almost certainly explains the high levels of resistance in the *H. contortus*, where the need to combat a highly pathogenic nematode has created a conflict with the sustainability of anthelmintic use. Where strategic control programs based on the seasonal absence of worm larvae on pasture explain high levels of anthelmintic resistance, it may be necessary to deliberately allow the survival of some worms not recently exposed to anthelmintics. In Western Australia, where the commonly-used “summer drenching” program provides excellent worm control but is associated with high levels of resistance in *T.circumcincta* and *Trichostrongylus* spp., the tactic of leaving a proportion of the flock undrenched when strategic treatments are given has reduced the development of resistance. However, the failure to suppress worms in summer has been shown to increase the risk of winter parasitism, especially in immature, worm-prone, animals (Besier and Love, 2003; Viviane et al., 2017).

In conclusion, considering the narrow range of currently available drugs and slow rate of new drug development, anthelmintic resistance presents an alarming global threat demands regular monitoring and management. The anthelmintic resistance against gastrointestinal nematodes is likely to be present in Ethiopian situation. Therefore, farmers should be educated on the risks of anthelmintic resistance and the need to utilize formal veterinary services in their vicinity, the quality of market available anthelmintic drugs should be evaluated both *in-vitro* and *in-vivo* and the brands of anthelmintic drugs that were tested and with proven efficacy should be used strategically so as to minimize the risk of development of resistance.

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