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Review Article

Review on Anthelmintic Drug Resistance of Nematodes in Ruminants and Methods of Detection

Tesfaye Rebuma[1*], Motuma Regassa[2], Firaol Tariku[2]

[1]School of Veterinary Medicine, Ambo University Guder Mamo Mezemir Campus Veterinary Teaching Clinic, Ambo, Ethiopia
[2]Nono Agricultural Office, West Shewa, Oromia, Ethiopia

Abstract
Anthelmintic resistance (AR) is described as a considerable improvement in the capacity of individuals within a strain of parasites to tolerate dosages of a substance that would be deadly to the vast majority of individuals in a normal population of the same species. The detection and monitoring of AR have been carried out using a variety of techniques, both in vivo and in vitro. All classes of antiparasitic medications have failed to work as intended due to frequent and improper use, which has resulted in an international AR crisis. When the same drugs are overused, AR is likely to emerge. This frequently results from underdosing, improper application of the drenching solution, and poor estimation of body weight. The issue of AR is a major one in Ethiopia and is frequently reported from many regions of the nation; nevertheless, the rural population is unaware of these issues with AR.
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Introduction

An issue that has global significance for effective parasite management is anthelmintic resistance (AR). It happens when worms can withstand a medicine at a typical dose and convey this ability to their progeny. Globally, the prevalence of anthelmintic medication resistance in livestock has been measured using diagnostic techniques with varying degrees of sensitivity (1). Reports of AR pose a threat to the survival of the cattle sector given how heavily farms rely on drugs to manage worms. Since resistant worms are becoming a major issue, modifications to current control strategies are urgently needed. The most effective approaches to preventing the development of AR involve reducing the pressure on medical professionals to prescribe specific medications and employ the proper timing to enhance their efficacy (2).

Modern gastrointestinal nematode control is based primarily on anthelmintics. The three primary chemical families of broad-spectrum anthelmintics previously used to treat gastrointestinal nematode infections were benzimidazoles, levamisole, other imidazothiazoles, and macrocyclic lactones. The "white drenches", "yellow drenches", and "clear drenches" are other names for each of the above-mentioned anthelmintics (3). The presence of AR is dependent on the host, the parasite, the kind of anthelmintic, animal management, and climatic conditions, which makes it more difficult to design preventive measures that should vary based on the animal production systems (4).

The development of AR, which is mostly brought about by the use of unconscious anthelmintics, also harms the economy. According to a definition that is more technically correct, resistance is the genetically determined decline in an anthelmintic ability to effectively combat a population of parasites that are typically sensitive to that medication. To kill 95% or more vulnerable parasite species, anthelmintics are often sold at dose rates that are many times higher than those needed. AR is evident when a population has a higher percentage of people who can tolerate drug doses than would be expected in a healthy population of the same species. The welfare and productivity of livestock are restricted globally by parasite-related infections. Anthelmintic medication is the mainstay of treatment for helminth infections (5).

A short time after the medicine was introduced, AR emerged due to heavy, unintentional drug use. Methods to identify AR were released by the World Association for the Advancement of Veterinary Parasitology (WAAVP) to raise awareness of this problem (6). An important issue today is AR, particularly in sheep. Several sheep and goat farms have been shut down because of multiple medication resistance in certain nations, including Australia, the United Kingdom, New Zealand, and South Africa (7,8).
Therefore, the objectives of this review were

- To review the AR in nematodes in general, including Ethiopia.
- To review methods of the detection of drug resistance of nematodes.

*Corresponding Author: Tesfaye Rebuma, Email: tesfayerebuma@gmail.com

- To overview factors affecting the development of AR.

Literature Review

Anthelmintic Drug Resistance

A rising issue in the world is parasite resistance to anthelmintic medications (9). The lowering of fecal egg counts, copro-antigen reduction tests, and egg hatch assays have all been used to demonstrate AR (10). An anthelmintic is a substance that kills helminths or makes them leave the digestive tract, as well as any other organs and tissues they may inhabit in their hosts. There are several safe anthelmintics on the market right now, some of which work against a variety of helminth diseases, while others have broader-spectrum efficacy. Many contemporary anthelmintics are effective against latent larvae as well as adults in the larval life cycle (11).

AR is the ability of the worm population or individual worms within the population to endure doses of an anthelmintic that would have otherwise killed a normal population of the same species and to pass on this resistant fitness to their progeny. A helminth population's accumulation of resistance genes occurs through an evolutionary process that is influenced by the genetic diversity of the parasite populations that are being selected for AR, the selection pressure (e.g., anthelmintic treatment), and time (12).

Anthelmintic medication given as chemotherapy or chemoprophylaxis is a major component of the treatment of parasitic helminths in domestic animals. Although all domestic species utilize anthelmintics, the ruminant market, particularly cattle, accounts for the highest market share, with millions of pounds being spent there each year to lessen the impacts of parasitism. Therefore, it is expected that parasite populations treated with anthelmintic medications will evolve progressively from totally vulnerable to fully resistant and at varied speeds under diverse situations (13).

AR can develop in several ways:

Side resistance: A parasite strain may be resistant to a dose of medications with a similar mode of action but a different chemical structure. For example, a parasite strain that is resistant to thiabendazole may also be resistant to fenbendazole. A distinction between resistance and tolerance should be made and noted. Tolerance is described as the midpoint between susceptibility and total pharmacological failure (14).

Cross resistance: It is similar to side resistance, but parasite strains can withstand therapeutic doses of drugs with different mechanisms of action or drugs with unrelated chemical structures. For example, a parasite resistant to benzimidazole will also show resistance to levamisole.

Multiple resistance: It occurs when parasites are resistant to two or more chemically unrelated anthelmintic groups due to independent selection by each group or through side resistance; for example, when a parasite resistant to thiabendazole also exhibits resistance to tetramisole, rafoxanide, and avermectin. Multidrug-resistant parasites exhibit resistance to various anthelmintic classes. For instance, *Haemonchus contortus* isolates exhibit multi-drug resistance to benzimidazoles and macrocyclic lactone anthelmintics (15).

Single resistance: It is one in which a single anthelmintic group exhibits resistant worms on a farm. If more than one worm species is involved in the resistance, the term multi-generic resistance is often used, i.e., if in a farm only Haemonchus contortus is resistant to benzimidazole, then it is termed single resistance, while if in a farm Haemonchus contortus, Trichostrongylus species, and Oesophagostomum species are resistant to benzimidazole, then it is a case of multi-generic anthelmintic resistance.

Dual resistance: It occurs when a farm raising cattle has worms that are resistant to one family of anthelmintics and another family of anthelmintics such as a farm where *Haemonchus contortus* is resistant to benzimidazole, but *Trichostrongylus* species is resistant to levamisole.

Reversion: An originally resistant strain of the parasite reverts to being susceptible to an anthelmintic.

Methods of Detecting Anthelmintic Resistance

The most popular technique for identifying and tracking the presence of AR in nematodes is the fecal egg count reduction test (FECRT), which is appropriate for all anthelmintics, even those that are metabolized by the host. Alternative methods of detection have also been developed, including several in vitro assays that track how anthelmintics affect the growth, development, or migration of worm stages. Both in vivo and in vitro methods can be used to detect the resistance to anthelmintics (Table 1).

Strategies to Prevent and Control the Anthelmintic Resistance

The creation and implementation of measures to stop the spread of AR, particularly in nematodes of sheep and goats, and stop it from becoming a problem in cattle, are urgently needed (16,17). The following methods will assist in maintaining anthelmintic effectiveness and reduce the issue of drug resistance.

Using full anthelmintic dosage: To avoid overdosing on some animals, it is preferable to adjust the dosage for the animal with the heaviest weight rather than for the average animal in the group. Worms with partial resistance are likely to survive at lower dosages (heterozygotes). They might then mate with worms that are similar to them, giving rise to highly resistant progeny (homozygotes) (18).

Rotation of anthelmintics: Since the frequent switching of anthelmintic types has historically resulted in the selection of multiple drug resistance, it is recommended to rotate drugs every year from different chemical families (e.g., avermectin, levamisole, and benzimidazoles).

Table 1. In Vivo and in Vitro Assays Used in the Detection of Anthelmintic Resistance

Bioassays	Spectrum	Type of Detection Method
Controlled test	All drugs	In vivo BA
Larval development	BZ, IV, LEV	In vivo BA
Larval paralysis	LEV, IV,	In vivo BA
Esterase activity	BZ	In vivo BA
Tubulin binding	BZ	In vivo BA
Egg hatch assay	BZ	In vivo BA
Tubulin probe	BZ	In vitro G
Egg hatch assay (larval paralysis)	LEV	In vivo BA
Egg count reduction	All drugs	In vivo BA

Note. BA: Bioassay; BC: Biochemical assay; G: Genetic assay; BZ: Benzimidazole; LEV: Levamisole; IV: Ivermectin. Source (4).

Avoiding high frequency of anthelmintic use: When depression is treated by giving sheep a dose every two to four weeks, susceptible worms are eradicated, leaving only resistant worms in the pastures.

Taking care in selecting anthelmintics: This is when the fecal egg reduction test comes in handy. It is crucial to bear in mind that some drugs with interconnected effects that have similar results can also have negative side effects such as resistance.

Developing strategic treatment programs: Fewer, epidemiologically based treatments will control worms just as effectively, be more cost-effective than ongoing treatments, and have less of a selection for drug resistance (19).

Synergism of anthelmintics: Sometimes combining medications can synergistically boost their efficacy. For instance, experimental mebendazole plus levamisole treatment in sheep in Australia boosted efficacy against benzimidazole-resistant worms. In the future, drug efficacy may be increased through the chemical alteration of already existing pharmaceuticals and new delivery technologies (20).

Genetically resistant hosts: The selection of flocks with parasite resistance genes could be accelerated by using new embryo splitting and transfer techniques. Worm resistance appeared to be highly heritable, and links between acquired resistance and specific lymphocyte antigen markers were detected (21).

Avoiding prolonged drug encounters: This can happen when using devices such as licks, blocks, or small-dose sustained-release rumen retention systems that gradually tail off the medication concentration. Due to its persistence at low quantities for several weeks following therapy, it might also happen with avermectin (22,23).

The Current Status of Anthelmintic Resistance in Ethiopia

In different regions of Ethiopia, different anthelmintics have been used to treat helminth parasites in sheep and goats. Anthelmintics have been used for an extremely long period, and they account for a sizable portion of the country's costs regarding helminthiasis control. Moreover, the misuse and trafficking of veterinary medications that contain anthelmintics are common in the nation. Some of these medications, most notably albendazole and tetramisole, have been consistently imported and supplied across the nation under various trade names and by various producers (24,25).

Regarding the status of AR in agricultural animals, scarce and inconsistent reports exist. *Oesophagostomum*, *Bunostomum*, and *Trichuris* parasites of goats in Adami Tullu have developed AR to tetramisole, despite the study's constrained and confined scope (26). In a study conducted in the Southern region of Ethiopia, the suspicion of resistance in small ruminant nematodes was observed (27,28).

In addition, some studies reported the prevalence of albendazole resistance in the nematodes of Stella State Farm crossbreed animals and moderate resistance in native Zebu cattle raised in large numbers in the Sebeta cities (29,30). For the treatment and management of helminth parasites in farm animals, anthelmintics are widely utilized across the nation. Due to a large number of illegal dealers and non-professionals that sell anthelmintics as common drugs on the open market, drug smuggling and the incorrect use of anthelmintics are quite frequent throughout the nation (31,32).

Conclusion and Recommendations

The lack of clear information on anthelmintic efficacy, susceptibility, or resistance on a regional and national basis, the lack of livestock owners and public awareness about the impact of AR on the economy of the country, the lack of a functional drug use policy, the lack of effective drug quality control, and drug smuggling are just a few reasons why AR warrants urgent attention in the current Ethiopian context. Therefore, everyone from the producer to the last person giving medication to animals could be blamed for the development of AR.

Studies on drug resistance can help to lessen its impact, and there are methods to improve the effectiveness or longevity of some medicines. When determining the prevalence of resistance in particular geographic areas or when treating individuals who have parasitic infections with resistant organisms, the ability to identify resistance can be helpful.

The following suggestions are therefore made in light of the aforementioned conclusion:

- Treatment schedules should be planned to avoid seasonal contamination buildup from parasites.
- Avoiding underdosing and making sure that therapies are completely effective are critical.
- Veterinarians should be assigned to each veterinary facility to properly administer anthelmintics.

- The focus should be on the issues of helminthiasis and AR at all levels.
- Public awareness of the issue of helminthiasis and the possibility of AR should be raised.
- It is necessary to create a practical drug policy.
- Anthelmintics should be taken on a yearly rotational basis.
- Animals should receive a precise dosage of their medications.

Authors' Contribution

Conceptualization: Tesfaye Rebuma, Motuma Regassa, Firaaol Tariku.
Data curation: Tesfaye Rebuma.
Formal analysis: Tesfaye Rebuma.
Funding acquisition: Tesfaye Rebuma.
Investigation: Tesfaye Rebuma.
Methodology: Tesfaye Rebuma, Motuma Regassa, Firaol Tariku.
Project administration: Tesfaye Rebuma.
Resources: Tesfaye Rebuma.
Software: Tesfaye Rebuma.
Supervision: Tesfaye Rebuma.
Validation: Tesfaye Rebuma.
Visualization: Tesfaye Rebuma, Motuma Regassa, Firaol Tariku.
Writing–original draft: Tesfaye Rebuma.
Writing–review & editing: Tesfaye Rebuma, Motuma Regassa, Firaol Tariku.

Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

Not applicable.

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