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Review on Anthelmintic Resistance in Gastrointestinal Nematodes of Small Ruminants

Mogos Mekonin, Walkite Furgasa and Tadesse Birhanu*

School of Veterinary Medicine, Collage of Medical and Health Science, Wollega University, P.O. Box 395, Nekemte, Ethiopia

***Corresponding author: drbirhan@yahoo.com**

Abstract: Gastrointestinal nematode parasitism is one of the major factors limiting sheep and goat production world widely because they cause heavy economic losses in meat and wool production. The wide spread use of antihelmintic for the control of gastrointestinal nematodes infections in the small ruminants has resulted in antihelmintic resistance. Antihelmintic resistance is a heritable change in the ability of individual parasites to survive the recommended therapeutic dose of antihelmintic drug. Among the classes of antihelmintic drugs currently in use, benzimidazoles is the first drugs to lose their effectiveness in nematodes of small ruminants, and antihelmintic resistance in sheep to thiabendazole was first reported. Resistance in worms can be the result of a variety of mechanisms and can be roughly categorized as genetic changes in the drug target, drug transport or drug metabolism. The most important factor in the development of resistance in veterinary helminthes to antihelmintic is the contribution of the worms, which survive treatment, make to the next generation. Fecal egg count reduction test and egg hatch tests are the method used to detect resistance to antihelmintic. The antihelmintic resistance is now considered the status quoin in most sheep-rearing countries. Therefore, appropriate control and prevention should be implemented.

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1. Introduction

The wide spread use of antihelmintic for control of nematodes infections in the small ruminants has resulted in antihelmintic resistance. Antihelmintic resistance can be described as a 'heritable change' in the ability of individual parasites to survive the recommended therapeutic dose of antihelmintic [1]. According to World Association for the Advancement of veterinary parasitology (WAAVP) antihelmintic resistance is defined as a failure to reduce fecal nematodes egg counts by at least 95% [2]. Antihelmintic resistance can also be understood 'as a decline in the efficiency of an antihelmintic against a population of parasites that is generally susceptible to that drug [3].

Resistances to various antihelmintic are observed in ruminants infected with gastrointestinal nematodes, due to constant use and improper use of some antihelmintic [4]. In fact, AR in gastrointestinal nematodes of small ruminant has been reported in different parts of the world [5], making it a seriously increasing problem [2,6]. Resistance to the major classes of antihelmintic has been recorded in Europe, Asia [7], North America [8], Latin America [9] and Ethiopia [10].

Ethiopia is home to 23.6 million sheep and 23.3 million goats [11]. Various antihelmintic have been used in different parts of the country for the treatment of sheep and goats helminthes parasites [12,13]. Helminthosis represents one of the constraints to livestock production in Ethiopia [14] by reducing production and reproductive performance. Antihelmintic resistance is now considered the status quoin in most sheep-rearing countries [15], and repeated cross-sectional studies in Europe and South America have shown a worsening situation, with both multi-drug and multi-species resistance increasingly more common [16].

Recently, two new classes of antihelmintic were launched, an amino-acetonitrile derivative, monepantel [17] and derquantel, which was marketed in association with abamectin [18]. However, there have been reports of resistance to monepantel [19,20] and to derquantel [21], indicating the high vulnerability of these drugs. Additional to the loss of effectiveness there are the effects of toxic residues on non- target organisms in the environment [22] and of residues in meat, milk and other animal products associated to antihelmintic [23].

Although the causes of helminthes parasitism in small ruminants are multiple and often interactive, the vast majority of cases are due to any of the following basic reasons; an increase in the number of infective stages on pasture, an alteration in host susceptibility, the introduction of susceptible stock into an infected environment, the introduction of infections into an environment, ineffective parasite removal from the host animals due to poor administration techniques and the use of sub-standard antihelmintic drugs and/or the development of antihelmintic resistance [24].

In our country, Control of gastrointestinal nematode parasites of livestock in smallholder farmer and pastoralist communities is done with limited antihelmintic drug use, or with traditional herbal remedies, and is performed mainly during the rainy seasons [25]. However, for smallholder farmers and stock owners in pastoralist communities, drugs are relatively expensive and are often not easily accessible, while frequent and indiscriminate use of different classes of antihelmintic has been reported in institutional and large commercial farms in Ethiopia [26]. Antihelmintic drug resistant is one of the major problem that quietly reflecting the small ruminant production qualities. Because this problem recently spread out in many areas all over the world, the alternative antihelmintic methods are recently requiring, especially using local economic plants or remedies for reducing the impact [27].Therefore, the object of this seminar paper was to review on antihelmintic resistance in sheep and goats and control and prevention of antihelmintic resistance in sheep and goat.

2. Literature Review

2.1 General overview of antihelmintics drug and mechanism of action

Antihelmintics are those drugs that are used in expelling out the worms that are parasitic in nature by either stunning them or by killing them. They are also known as vermifuges or vermicides. They are the broad and wide range of drugs and are separated into classes on the basis of similar chemical structure and mode of action. The anthelmintic efficacy of benzimidazoles is due to the ability of compromising the cytoskeleton through a selective interaction with beta-tubulin factor [28].

This showed the effects of benzimidazoles include the locomotion impairment, reproduction and a detrimental effect on oocytes with the disruption of processes thus requires the integral microtubules. Through this the molecular basis of benzimidazole molecule resistance has been investigated in the parasitic nematodes. The benzimidazole molecule showed resistance in different nematodes like *Haemonchus contortus* which is associated with the presence of specific alleles of beta tubulin in the drug. The specific beta-tubulin of worm could confers the resistance for the drug which was tested through experiments but this showed that the sensitivity of *C. elegans* mutants of benzimidazole can be rescued by expressing the *H. contortus* alleles of βtubulin from benzimidazole through which isolation was done [29].

Ivermectin is semi-synthetic derivatives of avermectin as antihelmintic in 1980 by Merck contain large macro cyclic lactones fermented product of the microorganism *streptomyces avermectilis.*

It is a potent drug and its discovery led to development of Ivermectin analogous which include moxidectin, milbemycin, oxime, doramectin, selamectin, abamectin and eprinomectin [30].

It causes the paralysis of pharyngeal and body wall musculature. Levamisole, pyrantel and morantel are the nicotinic receptor agonists which cause spastic muscle paralysis due to the prolonged activation of excitatory nicotinic acetylcholine (nAch) receptors on muscle [31].

3. Antihelmintic Resistance and Its Related Phenomena

Antihelmintic resistance is ability of worms to survive treatments that are generally effective at recommended dose rate is considered a major threat to the future control of worm parasites of small ruminants. Use of antihelmintic is the mainstay to reduce the adverse effects of these nematode parasites but their usefulness is constrained by the emergence of AR [32].

The clinical definition of resistance is 95% or less reduction in a “Fecal Egg Count” test. Treatment with an antihelmintic drug kills worms whose phenotype renders them susceptible to the drug. Worms that are resistant survive and pass on their “resistance” genes. Resistant worms accumulate and finally treatment failure occurs. Increased productivity in ruminants through the control of helminthes parasites will depend upon the availability of low cost, effective of antihelmintic [33].

3.1 Historical background of antihelmintic resistance

The world’s first report of AR involved the drug phenothiazine in sheep in the U.S. Among the classes of antihelmintic currently in use, benzimidazoles were the first drugs to lose their effectiveness in nematodes of small ruminants, and AR in sheep to thiabendazole was first reported. In goats, first reported resistance to benzimidazoles in the world occurred in the 1980s [34].

In the 1980s, macro cyclic lactones with endectocide activity were launched on the French market [35], and were soon thereafter launched in Brazil in various formulations and concentrations. The first report of loss of Ivermectin effectiveness in sheep was published in South Africa and was soon followed by reports in Brazil. Over time and with the use of new drugs, there have been numerous reports of resistances worldwide, especially in countries with a tradition of breeding small ruminants. In the absence of the release of new drugs, and given the increasing status of AR in small ruminants, combinations of drugs with different mechanisms of action began to be used in an effort to delay the development of resistance [2].

3.2 Mechanism of antihelmintic resistance

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 [6]. 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 does not seem to cause resistance to triclabendazole in *Fasciola hepatica* [36].

Even within a worm species different mutations can lead to resistance against the same antihelmintic. For instance, benzimidazoles resistance in *Haemonchus contortus* can commonly be caused by the phenylalanine to tyrosine mutation at amino acid position 200 of the isotype one beta-tubulin gene [29], however, the frequency of this major resistance point mutation varies considerably and it can be low even in resistant populations. Therefore, besides this point mutation, benzimidazoles (BZ)-resistant populations can carry different mutations that confer BZ-resistance. Furthermore, differences in drug transport or drug metabolism within a worm species also account for different resistance mechanisms against the same antihelmintic. On the other hand, as P-glycoprotein is able to transport many different drugs (including Ivermectin, benzimidazoles and imidazothiazole derivatives changes in this protein might confer cross-resistance to many other drugs [37].

3.2.1 Imidazothiazole /tetrahydropyrimidines

Resistance to LEV and the related imidazothiazole/tetrahydropyrimidines, such as pyrantel and morantel is a more complex issue. The target site of these nicotinic agonists is pharmacologically distinct nAChR channel in nematodes [38]. LEV is known to be a more potent agonist than acetylcholine at nematode muscle nAChRs [39]. The LEV receptors of nematodes, like those in vertebrates, are understood to be composed of five subunits that surround a central non-selective cation pore [40].

At therapeutic concentrations, LEV produces depolarization and contraction of nematode somatic muscle, which leads to paralysis and elimination of the parasite without affecting the host nicotinic receptors [41].

3.2.2 Macro cyclic Lactones

The major mechanisms helminthes use to acquire drug resistance appear to be through receptor loss or decrease of the target site affinity for the drug. Macro cyclic Lactones are established to modulate the glutamate-gated chloride (GluCl) channels that are found on membranes of the pharynx, somatic muscle and particular neurons of the helminthes [42]. The entry of IVM into the nematode is facilitated by sensory (amphidial) neurons located in the cephalic end of nematodes [43].

Once inside the cuticle, it specifically targets three families of the alpha subunits of GluCl channels [44]. GluCl channels found in insects, nematodes and crustacean, are not present in vertebrates, and are similar in sequence, and presumably analogous to the subunit A of gamma-amino butyric acid (GABAA) receptors [45].

3.2.3 Benzimidazoles

Unlike other antihelmintic, passive diffusion is a major mechanism of BZs penetration into the parasites, where lipid solubility is a determinant factor influencing the diffusion of these molecules through the parasite tegument [46].

BZs exert their effect by binding selectively and with high affinity to the beta subunit of helminthes microtubule protein, tubules, leading to subsequent disruption of the tubule–microtubule dynamic equilibrium. By binding to free beta tubules, BZs inhibit the polymerization of alpha and beta tubules molecules and the microtubule dependent uptake of glucose, resulting in paralysis and death. Molecular modifications in the beta tubules of the parasite are apparently the reason for resistance to BZs. Some tubules isotypes were found to be lost during selection for resistance resulting in the reduction of high affinity BZ-binding sites [47].

3.3 Factors affecting development rate of antihelmintic resistance

The most important factor in the development of resistance in veterinary helminthes to antihelmintic is the contribution that the worms, which survive treatment, make to the next generation. This in turn depends on the number of worms in refugia, that is, the numbers of worms that are not exposed to the drugs [48]. There are three main factors that influence the population of refugia; the numbers of larvae on pasture, the number of treated animals, and the extermination of all developmental stages within the host. Moving treated animals to rested pastures to minimize exposure to infective larvae has been recommended a useful method in endemic areas. However, these actions result in the next helminthes generation that consists almost completely of worms that survived therapy, and this practice is certainly responsible for the development of resistance. For example, problems with resistance are reported in the nematodes of sheep and goats on some Greek islands, which suffered from extended drought in contrast, no resistance developed under similar management and deworming practices on the mainland [16].

Especially the drench and move system, in which all animals in a flock are treated before they are moved to clean pastures containing few or no worms in refugia, is a strong selector of resistance. Only recently, it is realized that a balance has to be found between treatment efficacy and delaying the development of resistance. Only treating some animals on a farm has been proved to be very successful in delaying the development of resistance, although this might have some consequences on productivity [49].

A high treatment frequency selects for resistance is more strongly than do less frequent dosing regimens, and that resistance develops more rapidly in regions where animals are dewormed regularly. Even at these lower treatment frequencies, many cases of resistance have been reported especially when the same drug is used over many years [50].

Antihelmintic resistance is often first suspected in cases of apparent antihelmintic failure, but there are many factors that can be responsible for the lack of efficiency of a drug. These include: Under dosing: It can occur through improper administration of drugs, under estimation of weight, dilution of the drug for economic reasons, use of substandard drugs, enhanced drug metabolism by some types of animals, such as goats, or prolonged drug persistence, can contribute to selection for resistance [51].

***Rapid re-infection*:** If animals are grazed on heavily contaminated pastures, re-infection occurs immediately and this may give the impression of drug failure. This is particularly relevant where *Haemonchus contorts* is dominant, as it develops rapidly and is very pathogenic. *Inefficiency against arrested or dormant larvae*: Arrested larvae which are unaffected by the antihelmintic being used may continue development immediately after treatment. ***Presence of drug resistant parasites**:* Frequent regular treatments using the same antihelmintic given at low dosages over a prolonged period of time will predispose to the development of drug resistance [52].

3.4 Methods of detecting antihelmintic resistance

A number of techniques have been described to detect a presence of resistance to antihelmintic. These methods can be divided into *in vivo* and *in vitro* techniques. The in vivo methods are suitable for all types of antihelmintic, 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 [41].

3.4.1 In vivo techniques

The controlled efficacy test (CET) is seen as the "gold standard test "to calculate the true efficacy of antihelmintic [53, 54]. Control animals are infected with a known number of L3 and then dosed with antihelmintic at a range of concentrations. After a set time period, the animals are culled and worms recovered from the abomasums. Resistance is confirmed when the reduction in worm count is less than 90%, or more than 1000 worms survive treatment [1].

An untreated group is also included as a control. The use of test animals is expensive, time-consuming and labor intensive; there are also ethical concerns about the use of experimental animals [55]. The fecal egg count reduction test (FECRT) compares the fecal egg count of individual animals before and after antihelmintic treatment; it is relatively simple to perform and can be used to test all groups of antihelmintic, but like the CET, it is expensive and time-consuming [1]. A gap of 10-17 days, depending on the antihelmintic under test, between treatment and test days is required as a drop in egg production occurs directly after antihelmintic treatment. The inclusion of an untreated control group is recommended to identify any natural fluctuations in egg output during the test period. Resistance is confirmed when the reduction in fecal egg count post-treatment is less than 95% and when the lower 95% confidence interval of the reduction in fecal egg count is less than 90%. Resistance is suspected when only one of the two criteria is met [56, 57].

3.4.2 In vitro techniques

EHT only works with the BZs as LEV and the MLs are not ovicidal [54]. Eggs collected from feces are incubated in serial dilutions of TBZ and the percentage hatch rate observed. The EHT performs best on species of nematodes with rapidly hatching eggs [2].

In mixed gastrointestinal nematode infections, species identification of the hatched larvae is possible. Recently, a standardized protocol has been determined to allow easy repeatable comparison between laboratories [58]. An altered protocol for the egg hatch test is available for the detection of LEV resistance [49].

The micro-agar larval development test (MALDT) is used to identify resistance to BZs and LEV but cannot be used for the MLs as it is not reliable enough. The larval development test (LDT) can be used with any antihelmintic group and involves the development of L1 into L3 in the presence of the antihelmintic under test, with Escherichia coli as a food source [59].

A commercial larval development test called "drench rite" has been developed. Eggs collected from feces are allowed to hatch and the L1 are cultured in serial dilutions of antihelmintic for 2 hrs. The larvae feed on fluoresce in isothio cyanate-labeled *E. coli* and are incubated for a further 24 hrs. The numbers of larvae which fed or unfed at each antihelmintic concentration is determined by examining the larvae under a fluorescence microscope and this ratio compared to an untreated control group [60].

Another related assay for the detection of LEV and ML resistance is the larval migration inhibition test (LMIT) [61,62]. The exsheathed L3 are incubated in serial dilutions of antihelmintic and then placed, in solution, above a 25μm nylon mesh and incubated for a further two hours. Resistant worms, which have not been paralyzed by the drug, will be able to actively migrate through the mesh. By counting the number of migrated and non-migrated L3, the percentage migration can be calculated and, hence, provide an idea of an isolate's ability to survive antihelmintic treatment. In vitro assays are easier, faster and cheaper to perform than in vivo tests and do not require the use of animals, which also removes any inter-host variation [49].

4. Status of antihelmintic resistance in Ethiopia

Misuse and smuggling of antihelmintic in many forms such as illegal sales in open markets and irrational administration, is widespread in Ethiopia. In addition, due to the absence of methods that preserve and maintain the efficacy of antihelmintic, and delay or prevent the emergence of antihelmintic resistance are not practiced in any part of the country. Albendazole, broad-spectrum benzimidazoles is the most widely used antihelmintic for the treatment and prevention of nematode infections in sheep in Ethiopia. It is manufactured by many international factories with various trade names, imported and distributed by several agents to vast areas in Ethiopia [63].

The study conducted on small ruminant helminthes in eastern part of Ethiopia which identified the following genera's of nematodes parasites: such as *Haemonchus, Trichostrongylus,Bonostomum,Nematodirus, Oesophagostomum, Cooperia, Strongyloides, Trichuris and chabertia ovina* [64].

The antihelmintic resistance was occurring in Ethiopia. For example, research conducted in 2013 in the southern and western part of Ethiopia identified the resistance against Albendazole [10]. In the Eastern part of Ethiopia limited research was done on the antihelmintic resistance [26].

5. Prevention and Control of Antihelmintic Resistance

There is an urgent need for the development and adoption of strategies to prevent the spread of AR, particularly in nematodes of sheep and prevent it from becoming a problem. The following practical measures can be taken to delay the occurrence. These are, *Use the correct dose*, *Maintain drenching equipment;* a common cause for incorrect dosing is fault equipment. It is very important that equipment is tested for accuracy before the start of dosing. *Reduce dosing frequency*; is important to establish the epidemiology of the helminthes infections and introduce strategic deworming program based on a few well-timed treatments given when it is most advantageous. *Establish treatment and quarantine for all animals introduced to the farm*; it is advisable to keep the newly introduced animals isolated for 72 hrs after arrival and treatment. *Alternative treatment* ;Present information recommends continued use of an antihelmintic for at least a whole season (one year for many tropical and sub-tropical countries) provided it is effective. When changing the antihelmintic, a drug from a different class should be selected [52].

In addition farmers should consider establishing grazing management practices which reduce parasite burden and subsequently the need for treatment [53].

6. Conclusion and Recommendations

Antihelmintic Resistance (AR) in gastrointestinal nematodes of sheep and goats is seriously increasing problem and a global issue which reduce the product, productivity and increase the cost of treatment for disease. Increased AR in herds has led to the need to identify management practices that can reduce the impact of the problem, which requires a prior diagnosis of the situation.

Resistance to many antihelmintic has been observed in small ruminants infected with gastrointestinal nematodes due to constant use, mismanagement and improper use of some antihelmintic drug.

Thus, frequent and inappropriate treatments should be avoided. Moreover; further studies are needed to determine the antihelmintic resistance status of the different species of GINs in sheep and goats.

Competing Interests

The authors declare that there is no competing interest

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