Anthelmintic Resistance in Livestock Parasites: Indian Scenario

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A B S T R A C T

Parasitic diseases rank among the most prevalent infectious diseases. Chemotherapy forms the mainstay for control of parasites. Availability of antiparasitic drugs is limited due to high cost of development of newer drugs and rapid pace of development of resistance. Literature shows that resistance against all newly launched antiparasitic drugs is noticed within a decade time. Condition is severe and discouraging in tropical countries like India where animals carry substantial parasitic load and there is indiscriminate use of drugs. Anthelmintic resistance in helminthic parasites, particularly \textit{Haemonchus contortus} are well reported from India. Molecular markers are identified for large scale screening of benzimidazole resistance. Chemotherapy being central to the control of parasites, drug resistance is likely to be a major issue in near future. Constant surveillance and monitoring of antiparasitic drug resistance is the need of the hour. The problem of resistance can be circumvented either by delaying its onset or use of alternate strategies in the form of integrated parasite management.

Keywords

Anthelmintic resistance, benzimidazole and \textit{Haemonchus contortus}

Introduction

Antiparasitic drug resistance is the genetic ability of parasites to survive treatment with a drug that was generally effective against those parasites in the past. It is due to the selection of a specific heritable trait in a population of parasites that results into significant increase in survivability of that parasite population to standard recommended dose of the drug. After an animal is treated with an antiparasitic drug, the susceptible parasites die and the resistant parasites survive to pass on resistance genes to their offspring. Antiparasitic resistance poses a significant threat to animal health and can result into substantial production losses. Antiparasitic resistance has been documented in livestock, both globally and within India.

Many factors contribute to antiparasitic resistance, including the biology of the parasite; the immune status of the host animal;
treatment practices; drug properties; and certain livestock management practices. The situation has recently become alarming in India particularly anthelmintic resistance in the nematode parasites of grazing animals and acaricide resistance in livestock ticks. To help combat this emerging problem, there is a need to develop an antiparasitic resistance management strategy that promotes sustainable use of approved antiparasitic drugs by slowing the development of antiparasitic resistance in livestock parasites in India. This paper will mainly discuss anthelmintic and acaricide resistance in addition to throwing some light on drug resistance against protozoan parasites of livestock and poultry.

**Anthelmintic resistance**

Anthelmintics are a group of antiparasitic drugs that kill or expel parasitic helminth worms from the body of the host. Since 1940s anthelmintics remain mainstay of worm control and treatment of parasitic infections in farm animals. However, resistant parasitic population to majority of the launched anthelmintics are recorded within two decades of their commercialisation, for instances, phenothiazine launched in 1940s as first anthelmintic and its resistance report came into record by 1957 in USA (Drudge et al., 1957). Amongst livestock animals, sheep has witnessed maximum number of cases of anthelmintic resistance. In India, first report of anthelmintic resistance was published in 1976 from organised sheep farms of Uttarakhand region against phenothiazine and benzimidazole (thiabendazole) drugs (Varshney and Singh, 1976). Hitherto, the importance of anthelmintic resistance remained in dim light until 1990 when the condition become alarming and started reporting throughout India (Yadav, 1990). Globally, sheep was the main species of attention for the anthelmintic resistance until 1983, when the Kettle and co-workers reported first case of be benzimidazole resistance in goats (Kettle et al., 1983). The wonder drugs of 1980s, ivermectin was found to be ineffective against gastrointestinal nematodes in South Africa (Carmichael et al., 1987). Recently introduced anthelmintics such as derquantel and monepantel has also been reported to be ineffective in control of commonly found roundworm in small ruminants in certain parts of the world (Kaminsky et al., 2011; Scott et al., 2013). The emergence of anthelmintic resistance within a decade of their launch demonstrates the high vulnerability of these drugs. The following terms have been used while reporting resistance.

**Cross resistance**

Ability of the parasite strains to survive the recommended therapeutic doses of chemically unrelated drugs having different modes of action.

**Side resistance**

Parasites demonstrate resistance to a drug as a result of selection by another drug having similar mode of action.

**Multiple resistance**

Parasites are resistant to two or more anthelmintic groups because of either selection by each group independently or by side resistance.

**The current status of anthelmintic resistance in India**

There are over 100 reports from various states of India documenting development of anthelmintic resistance in livestock parasites against commonly used anthelmintic drugs. The anthelmintic resistance reports in India have been reviewed by several researchers...
There is paucity of information on anthelmintic resistance from the north east states of India (Table 1).

**The factors that have contributed to the development of anthelmintic resistance**

Anthelmintics form the mainstay of worm control in Indian conditions. Intensive and indiscriminate use has accelerated the development of anthelmintic resistance. Rate of development of anthelmintic resistance is influenced by genetic, biological, operational or environmental factors. Major factors that seek considerable attention are worm biology (includes genetic makeup, fecundity and generation interval), host parasite relationship (presence or absence of hypobiosis), environmental conditions (climate, worms on host or off host), drench frequency, under dosing, time of drenching, continuous use of drug with similar mode of action, influx of pharmaceuticals, borrowing of resistance (shared pasture or animal purchase), worm survival strategy, physiology of animals and anthelmintic pharmacology.

**The role of refugia in the management of anthelmintic resistance**

Refugia are the proportion of worm population which escapes exposure to any sort of anthelmintic drugs. It is the most important factor contributing to selection for anthelmintic resistance in parasites (van Wyk, 2001). It is only the parasitic sub-population (the parasites within the host) that can be exposed to any anthelmintic treatment. Worms that are in the free-living sub-population (eggs, L1, L2, L3) are not exposed to the anthelmintic and are said to be in refugia. Size of population in refugia at the time of anthelmintic treatment will determine the contribution of surviving susceptible worms to the subsequent generation. Worms in refugia provides a pool of genes susceptible to anthelmintics, thus diluting the frequency of resistance genes. As the relative size of refugia increases, the rate of evolution towards resistance decreases. The importance of refugia though varies between environment and seasons and while designing any deworming control one should consider the disadvantage of drenching an immune animal, drenching during dry season and drenching in situation of few or no worms in refugia. Nematodes in refugia come from three sources viz., pasture, untreated animals and inhibited stages surviving treatment in the host. Pasture contaminated with nematode larvae form an excellent source of nematodes in refugia so that continuously grazed pastures are less likely to permit the development of anthelmintic resistance provided that there is not heavy reliance on anthelmintic treatments (Coles, 2002).

**Mechanism of anthelmintic resistance**

Resistance in GI worms can arise due to target site insensitivity, metabolic detoxification or change in the drug transport (James *et al.*, 2009). In molecular studies, benzimidazole resistance in gastrointestinal nematodes is related with changes in the target site gene coding β-tubulin. Two distinct single nucleotide polymorphisms leading to changes in the amino acid sequence from phenylalanine (Phe, TTC) to tyrosine (Tyr, TAC) at position 167 (Silvestre and Cabaret, 2002), 198 (Ghisi *et al.*, 2007) and 200 (Kwa *et al.*, 1995) appears to play a major role in the mechanism of BZ resistance. Of these, F200Y mutation is common in *Haemonchus contortus* throughout the world. Although benzimidazole resistance appears in nematodes due to these mutations but the same mutation does not seem to cause triclabendazole resistance in liver flukes. In India, mutation at 200 position is most.
commonly reported followed by 198 position, however, 167 mutation never detected in Indian isolates (Sankar, 2007; Garg and Yadav, 2009; Rialch et al., 2014; Chandra et al., 2014, 2015; Saini et al., 2016). The mechanism of resistance to other anthelmintics has not been fully elucidated. Changes in P-glycoprotein and nicotine acetylcholinesterase receptor might be involved in ivermectin and levamisole resistance in gastrointestinal nematodes.

Methods for detection of anthelmintic resistance

The growing importance of anthelmintic resistance has led to an increased need for reliable and standardised detection method. Most of the methods described have drawbacks either in terms of cost, applicability and interpretation or reproducibility of findings (Varady and Corba, 1999).

The most widely used method for detecting and monitoring the presence of anthelmintic resistance in nematodes is the faecal egg count reduction test (FECRT), which is suitable for all types of anthelmintics including those that undergo metabolism in the host. In addition, a number of in vitro assays that measure the effects of anthelmintics on development, growth or movement of nematode stages have been developed as alternative methods of detection. Anthelmintic resistance can be detected by in vivo as well as in vitro techniques (Taylor et al., 2002).

The following in vivo tests are being used to detect anthelmintic resistance

Controlled test

This test is the most reliable method of assessing anthelmintic efficacy but also costly in terms of labour requirements and animal usage and is now rarely used. In an attempt to reduce the costs and time taken, laboratory animal models have been used (Taylor et al., 2002). To characterise the sensitivity of a field isolate, groups of worm free animals should be inoculated with infective larvae and the anthelmintic tested at 0.5, 1 and 2 times the recommended dose rate. Inclusion in the test of a known susceptible strain has been recommended. Resistance is generally confirmed when the reduction in geometric mean worm counts is less than 90%.

Faecal Egg Count Reduction Test (FECRT)

The FECRT provides an estimation of anthelmintic efficacy by comparing faecal egg counts of animals before and after treatment. A good correlation has been found between faecal egg counts and worm counts for Haemonchus contortus.

Various in vitro assays used for surveillance of anthelmintics resistance are as follows

Egg Hatch Assay (EHA)

Benzimidazole anthelmintics prevent embryonation and hatching of nematode eggs. A number of egg hatch/embryonation assays have been developed for the detection of resistance to this group of anthelmintics.

Larval Feeding Inhibition Assay

A larval feeding assay devised for detection of macrocyclic lactones and imidazothiazoles resistance in gastrointestinal nematodes (Alvarez-Sánchez et al., 2005). It is based upon the principle that the concentration of anthelmintic required to inhibit larval feeding in 50% of L1’s juvenile of nematode is higher in parasites resistant to either macrocyclic lactones or imidazothiazoles than those of susceptible isolates indicating development of resistance against these anthelmintics.
Table 1 State wise reports of anthelmintic resistance in livestock parasites in India

| State          | Year | Animal Species | Anthelmintic                          | References                     |
|----------------|------|----------------|---------------------------------------|--------------------------------|
| Jammu and Kashmir | 2012 | Sheep          | Benzimidazoles, Levamisole, Ivermectin | Itoo and Shahardar, 2012       |
|                | 2012 | Sheep          | Tetramisole                           | Itoo et al., 2012              |
|                | 2015 | Goat           | Benzimidazoles                        | Sharma et al., 2015            |
| Uttarakhand    | 1976 | Sheep          | Phenothiazine, Triclabendazole         | Varshney and Singh (1976)      |
|                | 1999 | Goat           | Benzimidazoles, Ivermectin            | Laha et al., 1999              |
|                | 2000 | Sheep          | Benzimidazoles                        | Yadav et al., 2000             |
|                | 2002 | Equines        | Benzimidazoles                        | Pal, 2002                      |
|                | 2004 | Goat           | Albendazole, Rafoxenide               | Hira Ram et al., 2004          |
|                | 2007 | Sheep          | Benzimidazoles, Imidathiazole, Salicylanilide | Garg et al., 2007 |
|                | 2012 | Sheep          | Benzimidazoles                        | Kumar et al., 2012             |
|                | 2013 | Sheep          | Benzimidazoles                        | Rialch et al., 2013            |
|                | 2014 | Equines        | Benzimidazoles, Ivermectin            | Kumar and Vatsya, 2014         |
| Haryana        | 1990 | Sheep          | Benzimidazoles                        | Yadav, 1990                    |
|                | 1992 | Goats          | Levamisole                            | Yadav and Uppal, 1992          |
|                |      | Goats          | Tetrahydropyrimidines, Levamisole, Morantel, Benzimidazoles | Uppal et al., 1992 |
|                | 1993 | Goat           | Benzimidazoles                        | Yadav and Uppal, 1993          |
|                | 1993 | Sheep          | Benzimidazoles, Morantel              | Yadav et al., 1993             |
|                | 1995 | Sheep          | Benzimidazoles, Levamisole, Morantel  | Yadav et al., 1995             |
|                | 1997 | Sheep          | Benzimidazoles                        | Chaudhari et al., 1997         |
|                | 1997 | Sheep and Goat | Benzimidazoles, Morantel              | Singh and Yadav, 1997          |
|                | 1997 | Cattle         | Morantel                               | Yadav and Verma, 1997          |
|                | 2000 | Sheep          | Oxyoclozanide and Tetramisole hydrochloride | Chaudhry, 2000 |
|                | 2003 | Sheep          | Closantel                             | Gupta et al., 2003             |
|                | 2004 | Sheep          | Benzimidazoles                        | Yadav and Garg,                |
| Year   | Region        | Animal | Drugs                  | Authors                     |
|--------|---------------|--------|------------------------|-----------------------------|
| 2005   | Punjab        | Sheep  | Rafoxanide, Morantel   | Das and Singh, 2005         |
|        |               | and Goat | Benzimidazole, Morantel |                             |
| 2007   | Punjab        | Sheep  | Benzimidazole, Tetramisole, Morantel | Chaudhari et al., 2007    |
| 2010   | Rajasthan     | Sheep  | Morantel, Ivermectin   | Singh and Gupta, 2010      |
| 2012   | Himachal Pradesh | Goat   | Benzimidazole          | Singh et al., 2012         |
| 2012   | Rajasthan     | Goat   | Ivermectin            | Singh and Poonia, 2012     |
| 2014   | Punjab        | Goats  | Benzimidazole, Ivermectin, Closantel | Vohra et al., 2014 |
| 2015   | Punjab        | Sheep  | Benzimidazole, Levamisole, Ivermectin | Sharma et al., 2015 |
| 2015   | Rajasthan     | Sheep  | Benzimidazole         | Singh et al., 2015         |
| 2016   | Rajasthan     | Sheep  | Benzimidazole         | Saini et al., 2016         |
| 2016   | Rajastan      | Sheep  | Fenbendazole, Levamisole, Morantel, Ivermectin | Kumar and Singh, 2016 |
| 2017   | Rajasthan     | Cattle | Fenbendazole, Ivermectin, Morantel, Levamisole | Singh, 2017               |
| 2012   | Punjab        | Sheep  | Fenbendazole, Ivermectin, Morantel, Levamisole | Buttar et al., 2012       |
| 2017   | Rajasthan     | Sheep  | Benimidazole          | Singh et al., 2017         |
|        | Rajasthan     | Sheep  | Benimidazole          | Singh et al., 1992         |
|        | Rajasthan     | Sheep  | Benzimidazole         | Swarnkar et al., 1993      |
| 1995   | Rajasthan     | Sheep  | Benzimidazole         | Singh et al., 1995         |
| 1996   | Rajasthan     | Sheep  | Rafoxenide,          | Singh et al., 1996         |
| 1996   | Rajasthan     | Sheep  | Benzimidazole, Levamisole | Gill, 1996               |
| 1999   | Rajasthan     | Sheep  | Benzimidazole, Levamisole, Rafoxenide | Swarnkar et al., 1999 |
| 2001   | Rajasthan     | Sheep  | Benzimidazole, Tetramisole, Rafoxenide | Swarnkar et al., 2001    |
| 2004   | Rajasthan     | Sheep  | Benzimidazole, Tetramisole | Swarnkar et al., 2004      |
| 2012   | Rajasthan     | Sheep  | Tetramisole           | Swarnkar and Singh, 2012  |
| 1995   | Uttar Pradesh | Sheep  | Tetramisole, Benzimidazole | Srivastava et al., 1995  |
| Year | Animal | Dose 1 | Dose 2 | Reference  |
|------|--------|--------|--------|------------|
| 2009 | Goat   | Benzimidazole, Morantel | Sharma and Rout, 2009 |
| 2012 | Sheep  | Benzimidazole | Kumar et al., 2012 |
| 2013 | Goat   | Ivermectin | Jaiswal et al., 2013 |
| 2014 | Sheep  | Benzimidazole | Chandra et al., 2014 |
| 2016 | Equines| Benzimidazole | Kumar et al., 2016 |
| 2012 | Goat   | Benzimidazole | Agrawal et al., 2012 |
| 2012 | Goat   | Levamisole | Kerketta et al., 2012 |
| 2014 | Goat   | Benzimidazole, Levamisole, Ivermectin | Kumar et al., 2014 |
| 2012 | Sheep  | Benzimidazole | Ghalsasi et al., 2012 |
| 2015 | Goat   | Benzimidazole, Levamisole, Ivermectin | Kumar and Kumar, 2015 |
| 1996 | Sheep  | Benzimidazole, Levamisole | Gill, 1996 |
| 2003 | Sheep  | Benzimidazole, Rafoxenide | Dhanlakshmi et al., 2003 |
| 2012 | Sheep  | Benzimidazole | Kumar et al., 2012 |
| 2016 | Sheep  | Benzimidazole, Levamisole, Ivermectin | Amulya et al., 2016 |
| 1996 | Sheep  | Benzimidazole, Levamisole | Gill, 1996 |
| 2005 | Sheep  | Benzimidazole, Levamisole, Morantel | Arunachalam et al., 2005 |
| 2005 | Sheep  | Levamisole | Sundaram et al., 2005 |
| 2009 | Sheep  | Benzimidazole, Levamisole, Ivermectin | Easwaran et al., 2009 |
| 2012 | Goats  | Benzimidazole, Levamisole, Ivermectin | Manikkavasagan et al., 2012 |
| 2013 | Sheep/Goat | Benzimidazole, Levamisole, Ivermectin | Arunachalam et al., 2013 |
| 2014 | Sheep  | Benzimidazole, Levamisole | Arunachalam et al., 2014 |
| 2014 | Sheep  | Benzimidazole | Meenakshisundaram et al., 2014 |
| 2015 | Goat   | Benzimidazole, Levamisole | Varadharajan and Vijayalakshmi, 2015 |
| 1996 | Sheep  | Benzimidazole | Gill, 1996 |
Larval Development Test (LDT)

Most anthelmintics affect the metabolism of a parasite in some way that affects parasite growth. In LDT, L₁ are cultured to L₃ in the presence of heat treated lyophilised *Escherichia coli*, as a food source, and the anthelmintic under test (Coles *et al.*, 1988). Suitable controls are also run without the presence of anthelmintic. Further a dose response curve is generated to determine LD₅₀ values.

Larval paralysis test

A larval paralysis test has been developed for the detection of levamisole and morantel resistance (Martin and Le Jambre, 1979). In the assay, infective third stage larvae are incubated for 24h in serial dilutions of the anthelmintic. After this time the percentage of paralysed larvae is determined at each concentration and a dose-response line plotted and compared to known reference strains (Alvarez Sanchez *et al.*, 2005).

Larva migration inhibition assay

L₃ obtained from larval cultures are isolated and stored in ventilated cell culture flasks at 6–10 °C in a fridge for a maximum of 3 months prior to use. LMIAs were performed before and (in case of a positive EPG) after treatment. L₃ are subjected to different concentrations of ivermectin and then migrated and non-migrated larvae are counted under a stereo microscope and the percentage of non-migrated larvae to the total amount of larvae are calculated (Demeler *et al.*, 2010).

Ways to maximize the effectiveness of anthelmintics

The main recommendation is to reduce the selection pressure for anthelmintic resistance in worm population by reduction in drench frequency, appropriate doses, alteration of anthelmintic classes and preferred use of narrow spectrum anthelmintics when possible depending on parasitic species. Another recommended approach is to follow target selective treatment (TST) instead of systematic ones. Diluting the alleles of resistance in worm populations could slow down the rate of selection of resistance. Goal of current research should be to translate the targeted treatment concept into practical.

Constant surveillance and monitoring of antiparasitic drug resistance in various common parasites of livestock and poultry is the need of the hour. The problem of resistance can be circumvented either by delaying its onset or use of alternate strategies.
in the form of integrated parasite management.

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