

Review Article

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Benzimidazole Resistance: An Overview

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ABSTRACT

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Anthelmintic drug resistant rising the major threat for the animal population. Benzimidazole group of anthelmintic drug are most popular and used drug in nematodal control strategy. High treatment frequency, single-drug regimens, targeting the mass treatments, under-dosing, improper use of anthelmintic, improper management, unguided and unaddressed policy of nematodal control leads to the resistant among the animal population which become main source of transferring and migrating the resistant to another. Selection pressure act majorly in escaping the treatment. Genetic as well as acquired factors are also play a role diversely in the resistance. Based on the current available knowledge and parameters, we have reviewed the epidemiological consideration of persistent prevalence, factors, and mechanism of benzimidazole (BZ) resistance which may further open the door for the researcher, investigator and policy maker for its control and standardizing the guideline.

Introduction

BZ resistance in gastrointestinal parasitism has been reviewed by many authors and particularly anthelmintic resistance in trichostrongylid nematodes have been thoroughly reviewed by Le Jampre (1978) and Prichard *et al.*, 1980. BZ resistance in GI parasitism has great epidemiological significance and there is also evidence that resistant parasites are more fecund, more pathogenic, increased establishment rates in

the host as well as survival in free living stages (Kelly *et al.*, 1977). BZ has been the mainstay drugs for the last five decades to control the Gastro-Intestinal (GI) nematodes, have resulted in the co-evolution of resistant parasites across the globe including India (Gill, 1996; Silvestre and Humbert, 2000; Garg and Yadav, 2009). Among different classes of anthelmintics, BZs are most widely used to control gastrointestinal nematode infections in small domestic ruminants due its high therapeutic index and ratio, absence of

drug residue in milk and meat and also economically viable (Humbert *et al.*, 2001). As a result of their continued use, resistance to BZ drugs has emerged world-wide within trichostrongylid parasitic nematodes including India (Gill, 1993; Waller, 1997; Jackson and Coop, 2000; Swarnkar *et al.*, 1999a, 1999b, 2001).

BZ resistance in strongyle nematodes are principally linked to alteration in the gene that encodes for β - tubulin isotype 1. This knowledge of the molecular basis of the resistance to xenobiotic has allowed the development of PCR based methods for their detection. Although numerous mutations of β -tubulin gene are candidates under experimental conditions, BZ-resistance in the three main gastrointestinal nematodes of sheep (*Teladorsagia circumcincta*, *Trichostrongylus vitrinus* and *Haemonchus contortus*) seems to be primarily linked to a point mutation in position 200 of isotope 1 β -tubulin gene, which replaces a phenylalanine (Phe) with a tyrosine (Tyr) (Kwa *et al.*, 1993a, 1993b, 1994, 1995; Elard *et al.*, 1996; Elard *et al.*, 1999). However, mutations at 167 (Phe to Tyr) and 198 (Glu to Ala) are also reported to be associated with resistance in some isolates (Prichard, 2001; Ghisi *et al.*, 2007; Rufener *et al.*, 2009). The codon 200 polymorphism has also been found in small strongyles (Cyathostominae) of the horse (Pape *et al.*, 1999; Von Samson-Himmelstjerna *et al.*, 2001). Based on polymorphism between resistance and susceptible population, several papers have described methods for genotyping different stages of the three trichostrongyloid species of sheep (Kwa *et al.*, 1994; Elard *et al.*, 1999; Silvestre and Humbert, 2000; Garg and Yadav, 2009; Chandra *et al.*, 2014, 2015) and in small strongyles (Von Samson-Himmelstjerna *et al.*, 2002a, 2002b). Allele specific PCR (AS-PCR) is effective method to identify point mutation (Silvestre and Humbert, 2000). Alvarez-Sánchez *et al.*,

(2005) performed real time PCR on isotype 1 of β -tubulin, strains of the main species of trichostrongylids (*T. circumcincta*, *H. contortus* and *T. vitrinus*) that are susceptible and resistant to BZ were differentiated.

Anthelmintic drug resistance

Gastrointestinal nematodes infections of livestock cause serious economic losses, in particular areas where extensive grazing is practiced. Fortunately, the availability of safe, broad spectrum anthelmintics have helped to reduce the incidence of great number of the worm diseases (Prichard, 1990). Modern anthelmintics are highly effective against the mature and immature stages of virtually all of the important gastrointestinal nematodes as well as many extra-intestinal nematodes. However, over rely on anthelmintics, extensive use and improper dosage of anthelmintics in conjunction with other factors has resulted in drug resistance, causing serious threat to effective control of helminth infections (Sangster, 1996).

Prichard (1980) defined resistance is present when there is a greater frequency of individuals within a population able to tolerate doses of a compound than in a normal population of the same species and is heritable. Side resistance exists, where the resistance to a compound is the result by selection by another compound with a similar mode of action. Cross-resistance resembles side resistance but involves compounds with different modes of action. Multiple resistance induced by multiple selection with anthelmintics same or different group has been demonstrated (Soulsby 1982). For instance, thiabendazole and parabendazole resistance parasites have been found to be cross resistance to other benzimidazole anthelmintics (Berger, 1975; Hall *et al.*, 1978). Multiple resistances occur when individuals are resistant to two or more different

anthelmintic groups either as a result of selection by each group independently or as a result of cross-resistance. Reversion is a decrease in the frequency of resistant individuals in a population following removal of the selecting agent.

Animals raised under grazing conditions are highly susceptible to various parasites and the primary control method is through the use of broad-spectrum anthelmintics (Waller, 1997). However, the indiscriminate use of these drugs without appropriate association with other methods to fight parasite infection has favored the development of helminth resistance to various drugs in the gastrointestinal strongyles of the small ruminants (Morales and Pino, 2001).

Development of anthelmintic resistance and its persistence

BZ's are believed to exert their effect on the parasites by binding to the tubulin protein and preventing it polymerizing into microtubules (Lacey, 1988). One critical question about BZ resistance concerns the origin of the BZ resistance alleles in worm population. These alleles may arise by spontaneous mutation or by migration. But anthelmintic resistance in nematodes is thought to be pre-adaptive phenomenon.

This implies that resistant populations are often considered to be present in the normal population as a rare allele prior to use of any drug. Studies with other models of resistance to xenobiotic demonstrated that migration plays a fundamental role in dispersion of insecticide resistance genes in mosquitoes (Raymond *et al.*, 1991), and of antibiotic resistance among some species of bacteria (O'Brien, 1997). In such cases, measures can be adopted to limit the spread of the resistance alleles. But, when the resistant alleles are present as a rare allele in a population, the

spread of resistance is more difficult to prevent since the anthelmintic treatments will inevitably constitute a selection pressure in favour of this rare alleles (Humbert, *et al.*, 2001). According to Wood and Mani (1981) the problem of resistance is multi-dimensional. It is a physiological or a biochemical property, its inheritance is genetical, the development of genetic strains is evolutionary and finally the evolution of resistance depends on ecological factors, which varies with species, population and location. Prichard (1990) summarized the intricate phases of the selected process such as susceptibility phase, intermediate phase and resistant phase. In susceptibility phase, the frequency of resistant individuals within the population is low. The intermediate phase develops when continued exposure to a drug, in which the frequency of heterozygous resistant individuals within the population increases. Finally, sustained selection pressure results in resistant phase, where the homozygous resistant individuals predominate within the population. The selection of resistant is most rapid when both heterozygous and homozygous resistant individual survive treatments.

Factors accelerating the resistance

Many factors are contributing the development of resistance, however frequent dosing of anthelmintics heads the list. Studies on nematodes (Round *et al.*, 1974; Barton, 1980, 1983; Martin *et al.*, 1982, 1984) clearly demonstrated that frequent dosing favours the resistance more strongly than less frequent dosing regimens. The reason is that the resistant genotypes are not affected by the treatment and continue to reproduce. While, the susceptible populations acquired from pasture are eliminated without reproducing offspring. Frequent dosing practice in goats has resulted in a high incidence of BZ resistance (Jackson, 1993).

BZ resistance has evolved in a variety of organisms and typically results from mutations in the β -tubulin locus at specific amino acid sites. β -tubulin mutations conferring resistance are generally recessive, frequencies of resistance alleles less than 30% would be difficult to detect on the basis of drug treatment failure (Bennett, 2002). When resistant is present at detectable levels in the field, the responsible alleles will be abundant in the gene pool due to the recessive nature of BZ resistance alleles in nematodes (Anderson *et al.*, 1998; Elard *et al.*, 1999).

Next to frequent dosing is under dosing. Under dosing favours the selection of resistant genes in a population of susceptible individuals (Coles *et al.*, 1992). Doses high enough to eliminate heterozygous genes for resistance render this trait become recessive, whereas under doses make effectively dominant (Roush and Mckenzie, 1987).

By using under doses, heterozygous individuals are allowed to survive and contribute resistant genes to subsequent generations. Another potential contributor to under dosing is where a single host harbour different type of parasites with different susceptibilities to a drug and the drug is used at the dose sufficient for more sensitive organisms on a spot basis. Inadequate attention to calibrate or condition of dosing equipment might be lead to delivery of under dose.

Management of parasites can contribute in a variety of ways to the generation of resistance. Cawthorne and Cheong (1984) reported that the movement of stock rather than use of anthelmintics as the main source of resistance. When introducing new animals from anthelmintic resistance prone areas to another farm without appropriate quarantine, disease monitoring, and treatment can rapidly sets in resistance problems.

Next, free living stages in the environment play a major role in enhancing the rate of development of resistance. Treatment was given, when the free living stages of parasite are susceptible to cold, reduction in the number of parasites in pasture, leaving the major source of subsequent infection to be the progeny of those worms which are resistant and survive treatment (Taylor, 1990; Sykes *et al.*, 1992).

But when the proportions of free-living worms are more, the offspring of the resistant worms will be diluted and resistance will be slow to develop.

The resistant worms have higher fecundity and increased establishment rates in the host than susceptible worms (Kelly *et al.*, 1978; Kelly and Hall, 1979). Dosing animals and moving them to clean pasture is essential for resistant control.

But, some researchers (Le Jambre, 1978; Taylor and Hunt, 1989; Smith, 1990) demonstrated that moving the animals to clean pasture after treatment favour the resistant gene selection. In this case, those worms that are resistant and survive treatment would be the major contributors to subsequent infection.

Physiological phenomena can also contribute to development of resistant population. In ruminant animals, the esophageal groove reflex can result in drug getting into an inappropriate compartment, where it is rendered ineffective or less effective resulting in enhanced rate of development (or) selection of resistant worms (Hennessy, 1994; Sanyal, 1994; Sanyal and Godke, 1996; Swarnkar *et al.*, 1999a; Singh *et al.*, 2002). Pharmacokinetics differences between individual animals and breeds of the same species can effect dose requirements and contribute to resistant population (Coles *et al.*, 1989; Sangster *et al.*, 1991).

Table.1 Reports of anthelmintic resistance from India

Region/Place	Host	Drug	Method	References
Northern India				
Uttar Pradesh	Sheep	Phenothiazine & thiabendazole	FECRT	Varshney and Singh, 1976
Haryana	Sheep	Benzimidazole	FECRT	Yadav, 1990
Haryana	Goat	Levamisole	FECRT	Yadav <i>et al.</i> , 1992
Haryana	Goat	Multiple except IVM	FECRT	Uppal <i>et al.</i> , 1992
Himachal Pradesh	Sheep	Benzimidazole	FECRT	Singh <i>et al.</i> , 1992
Haryana	Sheep	Multiple except IVM	FECRT	Yadav <i>et al.</i> , 1993
Haryana	Sheep	Benzimidazole	FECRT	Kumar and Yadav, 1994
Haryana	Sheep	Multiple except IVM	FECRT	Yadav <i>et al.</i> , 1995
Uttar Pradesh	Sheep	Benzimidazole & Levamisole	FECRT	Srivastava <i>et al.</i> , 1995
Uttar Pradesh	Goat	Benzimidazole	FECRT	Yadav <i>et al.</i> , 1996
Haryana	Cattle	Morantel	FECRT	Yadav and Verma, 1997
Haryana	Sheep & Goat	Benzimidazole	FECRT	Singh <i>et al.</i> , 1997
Uttar Pradesh	Goat	Benzimidazole	FECRT	Garg <i>et al.</i> , 2004
Uttar Pradesh and Uttarkhand	Sheep & goat	Benzimidazole	EHT, ASPCR	Sankar, 2003, 2007
Haryana	Sheep	Multiple	FECRT	Chaudhri <i>et al.</i> , 2007
Uttarkhand	Goats	Benzimidazole	FECRT	Ram <i>et al.</i> , 2007
Uttar Pradesh and Uttarkhand	Sheep	Benzimidazole	ASPCR	Garg and Yadav, 2009
Punjab	Sheep	Multiple	FECRT	Buttar <i>et al.</i> , 2011, 2012
Uttarkhand	Sheep and goat	Benzimidazole	FECRT EHA LDA	Rialch <i>et al.</i> , 2013
Uttar Pradesh	Sheep Goats	Benzimidazole	FECRT ASPCR	Chandra <i>et al.</i> , 2014, 2015
Central India				
Maharashtra	Sheep and Goat	Multiple	FECRT PCR-RFLP	Ghalsasi <i>et al.</i> , 2012
Chattisgarh	Goat and cattle	Multiple	FECRT EHT	Kumar <i>et al.</i> , 2014
Southern India				
Tamilnadu/Andhra	Sheep	Benzimidazole & Levamisole	FECRT	Gill, 1996
Tamilnadu	Sheep	Benzimidazole	FECRT	Jeyathilakan <i>et al.</i> , 2003
Tamilnadu	Sheep	Benzimidazole	FECRT EHT	Sundaram <i>et al.</i> , 2005
Tamilnadu	Sheep & goat	Benzimidazole	EHA, ASPCR	Sankar, 2003, 2007
Tamilnadu	Sheep	Benzimidazole & Levamisole	FECRT, EHA	Easwaran <i>et al.</i> , 2009
Kerala	Goat	Benzimidazole & Ivermectin	FECRT	Rajagopal <i>et al.</i> , 2013
Western India				
Rajasthan	Sheep	Benzimidazole	FECRT, EHA	Singh <i>et al.</i> , 1995
Rajasthan	Sheep	Refoxanide	FECRT	Singh <i>et al.</i> , 1996
Rajasthan and Gujarat	Sheep	Benzimidazole & Levamisole	FECRT	Gill, 1996
Rajasthan	Sheep	Benzimidazole, Levamisole & Refoxanide	FECRT, EHA	Swarnkar <i>et al.</i> , 1999a, 1999b
Rajasthan	Sheep	Benzimidazole & Refoxanide	FECRT, LDA	Swarnkar <i>et al.</i> , 2001
Rajasthan	Sheep	Benzimidazole	PCR-RFLP ASPCR	Tiwari <i>et al.</i> , 2006, 2007
Gujarat	Sheep	Multiple resistance including IVM	FECRT	Makvana and Veer Singh, 2009
Rajasthan	Goats	Multiple resistance including IVM	FECRT	Godara <i>et al.</i> , 2011
Rajasthan	Sheep	Benzimidazole and Levamisol	FECRT and EHT	Maharshi <i>et al.</i> , 2011
Eastern India				
West Bengal	Sheep & Goat	Benzimidazole	EHA, ASPCR	Sankar, 2003, 2007
Orissa	Goat	Multiple	FECRT	Sarangi <i>et al.</i> , 2014

Sheep and goats should not be kept on the same farm. The first reports of Ivermectin resistance in USA (Craig and Miller, 1990) and in New Zealand (Watson and Hosking, 1990) were derived from goats. Anthelmintic resistance was more common in goat farms (Kettle *et al.*, 1983) than sheep farms (McKenna, 1989). The rearing of goats with cattle reduce worm burdens (Bisset *et al.*, 1988), but resistant nematodes may be transmitted from goats to sheep if they are grazed together on the same pasture during the same year or in the spring and early summer of the following year. In these situations, goats are treated with higher doses than sheep (Coles *et al.*, 1989).

In India, anthelmintic treatment for sheep and goats, cattle and buffalo are grouped together and recommended similar dose rate. Sanyal and Godke (1996) reported that pharmacokinetics of BZ differs in sheep & goat and cattle and buffalo. Sanyal (1993, 1994) and Singh *et al.*, (2002) reported metabolism of BZ is faster in goats than sheep and buffalo than cattle. Thus, use of sheep dose in goats and cattle dose in buffaloes may enhance the selection pressure and favour to the resistant alleles. In India, farmers are not consulting their veterinary surgeons for managemental practices and they are treating their animals without correct information about anthelmintic dose. And also lack of knowledge of epidemiology of parasitic infection increases the spread of anthelmintic resistance to all over the country.

Extent of resistance to worldwide

Anthelmintic resistance has been developed against all classes of broad-spectrum anthelmintics and has been recorded from many countries throughout the world (Prichard, 1990; Jackson, 1993). Resistance against BZ is extensively reported in sheep and goats, and in some parts of the world it is

a serious problem. Van Wyk *et al.*, (1989) reported that the farmers in South Africa are getting out of business because there are no drugs are effective in controlling the multi-resistant nematode populations. Rolfe *et al.*, (1990) reports, "Resistance to anti-parasitic agents in sheep has emerged as the most important limitation for successful production of wool and meat in Australia". Waller *et al.*, (1996) suggested that anthelmintic resistance is wide spread in the high rainfall areas of East African countries such as Kenya, Tanzania, Zimbabwe and South American countries such as Argentina, Brazil and Uruguay. Resistance to anthelmintics could also become a problem for wildlife. The role of wild ruminants in spreading AR helminths has already been confirmed by Praslicka *et al.*, (1995). Among all anthelmintics, BZ resistance is the major problem and extensively reported from different countries (Van Wyk, *et al.*, 1989; Prichard, 1990; Taylor, 1990; Borgsteede, 1993). Since BZ resistance recorded in 1964, three years after thiabendazole (TBZ) was introduced biochemically (Drudge *et al.*, 1964). Many authors reported that the anthelmintic resistance in sheep nematodes from different countries. In New Zealand (McKenna *et al.*, 1990), South Africa (Van Wyk *et al.*, 1987; Van Wyk and VanSchalkwyk, 1990), England (Taylor, 1990; Coles *et al.*, 1988, 1992) Australia (Edward *et al.*, 1986; Waller *et al.*, 1996; Love *et al.*, 1992), Netherlands (Borgsteede, 1986, 1990) and France (Silvestre and Humbert 2000; Silvestre *et al.*, 2000, 2001; Humbert *et al.*, 2001), Canada (Barrere *et al.*, 2013), Brazil (Dos Santos *et al.*, 2014) and USA (Chaudhary *et al.*, 2014).

Earlier surveys and reports were restricted to single drug (or) single species of nematodes. Thereafter, the reports were extended to multi-generic resistance (Hall *et al.*, 1981; Barton *et al.*, 1985; Martin *et al.*, 1985; Bauer *et al.*, 1987; McKenna, 1989; Watson and

Hosking, 1990; Hong *et al.*, 1992) and multi drug resistance (Sangster *et al.*, 1979, 1985; Sangster, 1990, 1996; Van Wyk *et al.*, 1987, 1989; Jackson *et al.*, 1992; Love *et al.*, 1992; Uppal *et al.*, 1992).

Prevalence of anthelmintic resistance in India

Reports of anthelmintic resistance from India are scanty and scattered and also maximum reports are from farms based on conventional diagnostic methods (Table 1) also the maximum reports pertaining BZs, Levamisole and Rafoxanide, however, few reports of Ivermectin resistance are also available recent years.

Many of the earliest reports emanated from the northern India; however, later reports are also from other parts of the country and usually involved species with a high biotic potential such as *H. contortus*. Although the rate of emergence of resistant strains has generally been slower due to recessive in nature, the prevalence of resistance is also increasing throughout country particularly organised farm of small ruminants and horses.

The first report of AR in India by Varshney and Singh on 1976 at Sheep breeding farm, Pashulok, Rishikash, subsequent report of fenbendazole resistance was from sheep farm in Hissar, Haryana by Yadav (1990) followed by levamisole resistance (Yadav *et al.*, 1992). Hereafter, many reports were poured from many parts of the country particularly from Haryana, Rajasthan and Uttar Pradesh against all groups of anthelmintics except Ivermectin.

Since 2002, the prevalence of AR has been reported from all part of the country and few reports were based on advanced molecular techniques PCR-RFLP and AS-PCR (Tiwari *et al.*, 2006; Sankar, 2007; Tiwari *et al.*, 2007; Garg and Yadav, 2009; Rialch *et al.*, 2014;

Chandra *et al.*, 2014, 2015; Chaudhry *et al.*, 2015). However, our understanding of the genesis of anthelmintic resistance is meagre. Lack of concrete knowledge about epidemiology of parasites, unaware of AR particularly among farmers, inadequate facility to diagnosis and monitoring are the major issues in the area of anthelmintic resistance in India. Further, indiscriminate grazing system, diversity in climatic pattern, various agro-climatic zones with geographical variations and nomadic nature of sheep rearing are complicating the research on anthelmintic resistance.

Resistance to anthelmintic drugs in large and small ruminants has emerged as the most important limitation for successful production of milk, meat and other product. Basically the resistance has emerged very fast, even evolving its way to counter the drugs day by day. The field isolates are known to show resistance to all the available classes of anthelmintic. Historically, resistance has emerged rapidly in sheep and goat against each new class of anti-nematodal drugs. In some countries, situation is serious, that it has resulted in abandoning of livestock population.

Anthelmintic resistance coming up with alarming for the next generation for their survival, sustain and productivity. To counter the resistance, it required more basic research in the direction to find out the actual mechanism as well as their adaptive index which make them resistant in natural as well as in adverse conditions. Based on experience, some recommendations should be made by government to reduce the risk of development of drug resistance. The dramatic and rapid spread of resistance to all major classes of anthelmintics should be a warning against too strong a reliance on drugs in helminth control programmes in veterinary practice.

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