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Nematodes Resistance on Anthelmintics Group of Benzimidazole in Ruminants

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Abstract

One factor that inhibits the increase in ruminant productivity is nematode infection. It's cause a decrease in feed intake, weight gain, milk production, disease, death, and expensive medical expenses The control of gastrointestinal nematode infections in livestock, over the past decades is primarily based on the preventive or curative use of chemotherapeutics and generally uses broad-spectrum anthelmintic such as benzimidazole, probenzimidazole, imidazothiazole, macrolide and ivermectin. The widespread use of several antelmintic groups now causes an increase in the incidence of gastrointestinal nematodes resistance against anthelmintics. Anthelmintics derived from various types of plants are expected to replace the benzimidazole so that it can reduce the level of resistance of the gastrointestinal nematodes in ruminants. However, for the future there is still a lot of research needed to further improve the ability of natural medicinal drugs to cope with gastrointestinal nematode infections in ruminants.

Keywords: benzimidazole, nematode,resistance, ruminants

Introduction

Gastrointestinal nematodes are one of the inhibiting factors for increasing the productivity of ruminants because they can cause a decrease in feed intake, weight, milk production, disease, death, and high medical costs incurred (Waller and Prichard, 1986; Githigia et al., 2001 ; Papadopoulos et al., 2012). Nematodes will be quite detrimental to other ruminants by destroying intestinal epithelial cells so that they interfere with nutrient absorption, host blood sucking, mineral retention, interfere with protein metabolism and in excessive amounts can lead to blockage of the digestive tract (Donald et al., 1978; Robert and Kyriazakis, 2001) Clinical symptoms that appear include anorexia, emaciation, diarrhea and end in death, whereas the results of blood tests in animal sufferers usually experience anemia, hypoproteinemia and hypoalbuminemia (Silvestre et al., 2000; Akanda et al., 2014). However, the determination of the degree of nematode infection depends on the age of the host, infecting nematode species and animal physiological status (Bekele, 1993; Tembely et al., 1997).

Nematodes which are often found in the ruminant gastrointestinal tract are H. Contortus, Trichostrongylus spp, Nematodirus spp Cooperia sp., Bunostomum sp., Mecistocirrus sp. and Trichuris sp, Thelazias pp and Ascaris spp (Roeber et al., 2013; Junaidi et al., 2014; Hossain et al., 2016). Efforts that can be done to reduce losses due to gastrointestinal nematode infection are by eradicating and controlling parasites (Pomroy et al., 2002; Crawford et al., 2006). Control of gastrointestinal nematodes in livestock generally uses broad-spectrum anthelmintic such as benzimidazole, probenzimidazole,

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imidazothiazole, macrolide and ivermectin (Campbell et al., 1983; Adediran and Uwalaka, 2015; Hamad et al., 2017). The widespread use of several anthelmintic groups currently causes an increase in the incidence of gastrointestinal nematodes against anthelmintics so that it is necessary to control them regularly and periodically for livestock (Redman et al., 2015). At present the resistance to the benzimidazole class antelmentic has occurred in almost all over the world and its prevalence continues to increase from year to year. This is evidenced by the large number of studies and cases in the field regarding the prevalence of resistance of nematodes to benzimidazole anthelmintics (Kwa et al., 1995; Sangster and Gill, 1999; Soutello et al., 2007; Gasbarre et al., 2009). The report on the resistance of nematodes to benzimidazole groups in ruminants has occurred in many countries such as Australia (Playford et al., 2014), New Zealand (McKenna, 1996), Mexico (Torres-Acosta et al., 2003), Brazil (Jaeger and Carvalho -Costa, 2017), Argentina (Mejı´a et al., 2003), Kenya (Waruirua et al., 1998), Ethiopia (Sheferaw and Asha, 2010), England (Stafford et al., 2007), France (Chartiera et al., 1998), Germany, Sweden (Demeler et al., 2009), Pakistan (Hamdullah et al., 2015), United States (Gasbarre et al., 2009). Whereas in Southeast Asia the problem of resistance of nematodes to benzimidazole groups in ruminants has been reported in Indonesia (Dewi et al., 2017), Thailand (Kochapakdee et al., 1995), Malaysia (Dorny et al., 1994), and the Philippines (Ancheta et al., 2004). This paper aims to provide a brief study of gastrointestinal resistance to the benzimidazole class anthelmintics and their control and alternative treatments to reduce the level of resistance.

Treatment of gastrointestinal nematodes with benzimidazole

Benzimidazole is an organic aromatic heterocyclic compound and has a variety of medical and biological activities, such as antitumor, antibacterial, antifungal, antiviral, anticonvulsant, antidepressant, analgesic, anti-inflammatory and antidiabetic (Alasmary et al., 2015). Benzimidazole derivatives are albendazole, fenbedazole, triclabendazole, oxfendazole, mebendazole and are widely used to treat infestations of nematodes and trematodes in livestock (Vercruysse and Claerebout, 2001). Gastrointestinal nematodes are found in ruminants and can result in low productivity and in severe conditions can even cause the death of young ruminants (Paddock, 2010; Velde et al., 2018). In contrast, old ruminants are resistant to gastrointestinal nematode infections because they have a higher body resistance compared to young ones so that striking clinical symptoms are rarely seen (Charlier et al., 2009; Bennema et al., 2010). Reports in the field suggest that in general infections of the gastrointestinal nematode cause clinical symptoms such as decreased appetite and weight, general weakness, pale

conjunctiva, anemia and diarrhea (Hunter, 1996). Taylor et al. (2007) added that in general the condition of livestock infected with gastrointestinal nematodes would be more severe if the quality of feed consumed was low because it would result in a decrease in overall immune system. Some of the most common types of gastrointestinal nematodes in small ruminants are Haemonchus spp, Trichostrongylus spp and Oesophagostomum spp. (Thomas et al., 2007; Suarez et al., 2017). According to Levine (1994), the gastrointestinal nematodes most commonly found in large ruminants are Haemonchus contortus, Bunoston phlebotomum, Strongyloides papillosus, Trichostrongylus axei, Toxocara vitulorum, Oesophagustomum raditum, Nematodirus filicollis, Cooperia punctata and Trichuris ovis. Around 15 billion US dollars per year worldwide is spent on livestock production costs and 27% of these costs are used to combat parasitic infections (Jaeger and Carvalho-Costa, 2017). In order to reduce the high cost, an integrated handling is needed so that it is expected to get maximum results.

Progress in the development of anthelmintic drugs has a significant contribution to the reduction in the cost of maintaining maintenance of ruminants due to gastrointestinal nematode infections. Currently there are 3 most widely used anthelmintic groups in the world, namely benzimidazole, imidazothiazoles and macrocyclic lactones. The three anthelmintic groups have been shown to be able to prevent, reduce and control gastrointestinal nematode infections in ruminants. Benzimidazole derivatives that have been circulating and are widely used in the field are albendazole, fenbedazole, triclabendazole, oxfendazole, mebendazole.

The benzimidazole group has many benefits and advantages such as low toxicity in mammals, broad spectrum, high efficacy, easy application and relatively inexpensive prices (Lacey, 1990; Lanusse and Prichard 1993; MacDonald et al., 2004; Jean et al., 2016; Enejoh and Suleiman, 2017). According to Haryuningtyas et al. (2001), in the last ten years the worm medicine for ruminants which was most marketed in Indonesia was from the benzimidazole group. Table 1. shows the use of the benzimidazole group for the treatment of gastrointestinal nematode infections in large and small ruminants. In Table 1 it can be seen that the benzimidazole group is still widely used and is quite effective in dealing with infections of the gastrointestinal nematodes in large and small ruminants. In table 1 it is also seen that dosing and application are in accordance with the recommended rules. However, many results of studies showing high levels of resistance of gastrointestinal nematodes to antelminthic benzimidazole groups have raised concerns among many parties related to pharmaceutical and livestock industries throughout the world.

Table 1 Use of benzimidazole derivatives for the treatment of gastrointestinal nematodes in ruminants

Type of medicine	Dosage form	application	Nematoda	Livestock	Reference
Albendazole	Bolus	7,5 mg/kgBB, oral	*0. ostertagi, Trichostrongylus axei, dan Cooperia oncophora*	Bovine	Borgsteede, 1979
Mebendazole	Bolus	52 mg/kg BB, oral	*H. contortus*	Sheep	Bennet *et al.,* 1980
Tricabendazole	Bolus	12 mg/kgBB oral	*Fasciola hepatica*	Bovine	Shi *et al.,* 1989
Triclabendazole	Bolus	12 mg/kg, oral	*Fasciola hepatica*	Bovine	Richards *et al.,* 1990
Mebendazole	Bolus	52 mg/kg BB, oral	*Haemonchus, Trichonstrongylus, Ostertagia*	Sheep	Farias *et al.,* 1997
Albendazole	Solution 2%	3,8 mg⁄kg BB,intravena	*Nematoda gastrointestinal*	Sheep	Alvarez *et al.*, 2008
Albendazole	Bolus	3,5 mg/kgBB, 0rql	*Haemonchus spp. Trichuris spp., dan Strongyloides papillosus*	Sheep	Kumsa *et al.,* 2010
Fenbendazole	Bolus	7,5 mg/kgBB	*Haemonchus spp. Trichostrongylus, Oesophagostomum Bunostomum dan Strongyloides spp.*	Goat	Godara *et al.,* 2011
Oxfendazole	Bolus	30mg/kgBB	*F. hepatica*	Sheep	Gomez-Puerta *et al.,* 2012
Albendazole	Bolus	7,5 mg/kg BB, oral	*Haemonchus sp., Mecistocirrus sp., Trichuris sp., Trichostrongylus sp., Oesophagostomum sp.* dan *Bunostomum sp.*	Bovine	Islam *et al.,* 2015
Albendazole	Fluid	1 ml/5 kg BB	*Ostertagia*	Sheep	Puspitasari *et al.,* 2015
Albendazole	Bolus	7,5 mg/kg BB, oral	*Haemonchus spp, Trichostrongylus spp , Cooperia spp., Oesophagostomum sp p., Trichuris spp., Strongyloides spp*	Goat	Aktaruzzaman *et al.,* 2015
Fenbendazole	Bolus	5 mg/kg BB, oral	*Haemonchus* dan *Cooperia*	Sheep	Holsback *et al.,* 2016
Albendazole	Bolus	7,5 mg/kg BB, oral	*Haemonchus, Cooperia, Trichuris, Trichostrongylus, Teladorsagia, Bunostomum and Strongyloides*	Sheep	Seyoum *et al.,* 2017
oxfendazole	Bolus	5.0 mg/kg BB oral	*Trichostrongyle, Ostertegia, Haemonchus, Cooperia, Paracooperia dan Nematodirus.*	Bovine, buffalo	Reddy *et al.,* 2017

Resistance of the gastrointestinal nematode benzimidazole group

Antelmintic resistance is defined as the ability to tolerate anthelmintic doses in parasitic populations that should have the ability to kill normal populations of the same species (Prichard et al., 1980). Intensive use of the benzimidazole group since 1970 caused the selection of parasite populations that were resistant to several animal species and thus became a worldwide problem in livestock, especially small ruminants such as sheep and goats. According to Zajac and Gibson (2000), nematodes have the genetic ability to develop anthelmintic resistant properties, giving rise to resistance to these drugs. Until now various methods have been developed for the diagnosis of gastrointestinal nematode resistance tests

and can be classified into in vitro and in vivo methods (Taylor et al., 2002). Several in vitro resistance tests that have been carried out are egg hatch assay (EHA), larval development assay (LDA), larval feeding inhibition assay (LFIA), micromotility meter test (MMT) and larval motility inhibition assay (LMIA) (Lorimer et al ., 1996; Tandon and Kaplan, 2004; Himmelstjerna et al., 2009; Demeler et al., 2012; Holm et al., 2014). stated that the resistance test of nematodes to anthelmintics in ruminants recommended by the World Association for Advancement of Veterinary Parasitology (WAAVP) and stated as the gold standard is a faecal egg count reduction test (FECRT) in vivo (Coles et al. 1992; Flanagan et al. , 2011; Belina et al., 2017). Varady and Corba (1998) add that the test becomes more complete and accurate when combined with in vitro test methods such as egg hatch test (EHT), and larval development test (LDT) to evaluate the development of resistance to the anthylmintic benzimidazole group in the field. Wood and Mani (1981) summarize these factors into four groups, namely genetic, reproductive, ecological and operational factors. While according to Medeiros (1997) and O'Brien (1997), the resistance of gastrointestinal nematodes to benzimidazole can occur through 3 phenomena, namely the transfer of resistant genes from one population to another, the presence of previously resistant alleles and spontaneous mutations. Silvestre et al. (2000) and Silvestre and Cabaret (2002) state that the spread of gastrointestinal nematode resistance to the benzimidazole group in a population can be caused by various factors. Furthermore according to Lacey, (1988) the molecular mechanism of resistance to benzimidazole in nematodes involves a single gene that encodes the β tubulin isotype-1 gene. Some mutations in the b-tubulin isotype-1 gene, which encode the target drug have been shown to be strongly associated with gastrointestinal nematode resistance (Kwa et al., 1995). According to Elard and Humbert (1999) and Silvestre and Humbert (2002), substitution of phenylalanine for tyrosine at positions codons 167 and 200 (F167Y and F200Y) of isotype-1-tubulin has been reported in H. contortus and T.circumcincta and acid substitution glutamate for alanine at position 198 (E198A) in H. Contortus.

According to Jaeger and Carvalho-Costa (2017), livestock grazing and defecating in the same place have the potential to experience recurrent gastrointestinal nematodes due to the use of benzimidazole as a routine treatment to control nematodes and ultimately cause the process of spreading resistance. The results of Barton (1983) study show that repeated anthelmintic use has the potential to cause anthelmintic resistance. Reports of the resistance of gastrointestinal nematodes to the benzimidazole group in ruminants have occurred in almost all parts of the world as shown in Table 2.

Table 2. Gastrointestinal nematode resistance to benzimidazole groups in various countries.

Type of medicine	Nematoda	Livestock	Country	Reference
Albendazole	*Ostertagia spp dan T. Colubriformis*	Sheep	Australia	Anderson *et al.,* 1991
Fenbendazole	*Ostertagia circumcincta*	Goat	Scotland	Jackson *et al.,* 1992
Albendazole dan oxfendazole	*Haemonchus contortus*	Goat	Malaysia	Dorny *et al.,* 1994
albendazole, fenbendazole, oxfendazole	*Haemonchus contortus*	Goat	Malaysia	Rahman, 1994
albendazole, fenbendazole	*Haemonchus sp. Trichostrongylus sp*	Goat	Thailand	Kochapakdee *et al.,* 1995
Oxfendazole	*Cooperia oncophora and Ostertagia ostertagi*	Bovine	New Zealand	Hosking *et al.,* 1996
Oxfendazole	*Haemonchus sp. Trichostrongylus sp, Cooperia sp., Oesophagostomum sp., Ostertagia sp*	Sheep	Brazilia	Thomaz-Soccol *et al.,* 2004
Albendazole	*Cooperia spp*	Bovine	New Zealand	Waghorn *et al.,* 2006
albendazole	*O ostertagi, Cooperia spp*	Bovine	New Zealand	Pomroy, 2006
Oxfendazole	*Haemonchus contortus, Trichostrongylus colubriformis, Cooperia curticei, Teladorsagia circumcincta dan Oesophagostomum spp.*	Goat	Pakistan	Saeed *et al.,* 2007
Albendazole dan fenbendazole	*Nematodirus dan Trichuris*	Sheep	Czechoslovakia	Vernerova *et al.,* 2009
Albendazole	*Haemonchus placei and H. Contortus*	Bovine	United States of America	Gasbarre *et al.,* 2009
Albendazole	*Haemonchus dan Oesophagostomum*	Bovine	Brazilia	Costa *et al.,* 2011
Fenbendazole	*H. contortus*	Goat	Denmark	Holm *et al.,* 2014
Fenbendazole	*H. contortus*	Goat	India	Das *et al.,* 2015
Fenbendazole	*Strongyle spp*	Goat, Sheep	India	Singh *et al.,* 2017
Albendazole and fenbendazole	*Haemonchus spp. by Trichostrongylus spp., Camelostrongylus mentulatus, Ostertagia ostertagi dan Cooperia spp*	Alpaca	Australia	Rashid *et al.,* 2018

The report is quite alarming and raises concerns among various groups involved in the livestock industry. At present the livestock industry is increasingly threatened by diseases caused by gastrointestinal parasites because of the increased resistance of drugs used for treatment and control (Sargison et al., 2005; Woodgate et al., 2017). Table 2 shows that many gastrointestinal nematodes in large and small ruminants have become resistant to benzimidazole drugs. The occurrence of resistance to anthelmintic is thought to be caused by a variety of factors that influence the non-optimal dose, irregular frequency of administration, uncontrolled use of drugs, administration of drugs from the same group for long periods, improper application and

rotation not appropriate for anthelmintic use (Carmichael, 1993; Waller et al. 1995; Molento, 2009; Maroto et al., 2011; Rialch et al., 2013). In conditions in the field where there are detected cases of gastrointestinal nematode resistance to benzimidazole drugs, further studies are needed to observe the effectiveness of treatment so that different treatment strategies can be determined which are expected to be more effective (Silvestre and Humbert, 2002; Miller et al., 2012, Borges et al., 2013). Various suggestions, suggestions and efforts to inhibit the spread of gastrointestinal nematode resistance to benzimidazole drugs have been done. Several attempts have been made to overcome the emergence of gastrointestinal nematode resistance to benzimidazole drugs. One of these efforts is by giving anthelmintic different compounds or groups or a combination of both (Anderson et al., 1991; Ramos et al., 2016). Another effort to overcome the problem of resistance is the use of natural anthelmintic drugs.

Natural anthelmintic derived from plants has been widely used to overcome nematode infestations in ruminants with varying results. Natural anthelmintic can be used singly or in combination. Natural anthelmintic derived from plants include Calotropis procera (Iqbal et al., 2005), Trachyspermum ammi (L.) flowers (Lateef et al., 2006), Nicotiana tabacum L (Iqbal et al., 2006), Biophytum petersianum Klotzch or kebar grass (Baaka et al., 2017), Azadirachta indica (Jamra et al., 2015), Butea frondosa (Qadir et al., 2010) and A. Senegalensis (Alawa et al., 2003).

Widyani et al. (2016) used a combination of 20% mango meeting, 20% turmeric, 20% comedy meeting and 40% kakys fruity enzyme to prevent helminthiasis in beef cattle. His results showed that the combination could reduce endoparasitic infestation from 220 EPG to 20 EPG after 4 weeks of treatment. Sunandhadevi et al. (2017) uses a combination of Vernonia anthelmintica, Artemisia maritima, Butea frondosa and Holarrhena antidysentrica for the treatment of gastrointestinal nematodes in goats. The combination of Nicotiana tabacum, Azadirachta indica, Calotropis procera, Trachyspermum ammi was used by Gupta et al. (2017) for the treatment of gastrointestinal nematodes in goats. Anthelmintik from various types of plants is expected to replace the benzimidazole anthelmintic so that it can reduce the level of gastrointestinal nematodes in ruminants. However, for the future there is still a lot of research needed to further improve the ability of natural medicinal drugs to cope with gastrointestinal nematode infections in ruminants.

Conclusion

An increase in the prevalence of resistance to the benzimidazole group antelmentic increased from year to year. This is due to several factors, including the non-optimal dose, the frequency of irregular

administration, the use of drugs as an uncontrolled prevention, the administration of drugs from the same group for a long time, improper application and improper rotation on the use of anthelmintic . Natural anthelmintic derived from plants has been widely used to overcome nematode infestations in ruminants and is expected to reduce the level of resistance of gastrointestinal nematodes to benzimidazole groups in the future.

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