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Effectiveness of Ivermectin and Albendazole against *Haemonchus contortus* in Sheep in West Java, Indonesia

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Abstrak: Memberikan dos separuh antelmintik merupakan suatu kaedah untuk mengesan daya tahan parasit yang menjangkiti haiwan ruminan kecil. Apabila satu antelmintik tidak berkesan dalam kambing biri-biri asal daripada Indonesia, satu kombinasi antelmintik daripada kelas kimia berbeza dengan cara tindakan berbeza diberikan sebagai satu strategi pengawalan parasit alternatif. Kajian ini membezakan kemujaraban antelmintik ivermectin (IVM) dan albendazole (ABZ) yang diberikan secara berasingan ataupun separuh dos ataupun diberikan bersama kepada kambing biri-biri yang dijangkiti secara semula jadi dengan *Haemonchus contortus*. Dua belas kambing biri-biri daripada Bogor, Jawa Barat, Indonesia telah dibahagikan kepada enam kumpulan rawatan: dos separuh IVM, dos penuh IVM, dos separuh ABZ, dos penuh ABZ, kombinasi IVM + ABZ, dan kawalan. Kemujaraban rawatan telah ditentukan menggunakan ujian pengurangan pengiraan telur tinja (FECRT) pada hari 0 (pra-rawatan) dan pasca-rawatan pada hari-hari 7, 14, 21, 28, 35, dan 42. Kemujaraban separuh dos IVM, dos penuh IVM, dos separuh ABZ, dos penuh ABZ, dan rawatan kombinasi bernilai daripada –1900% hingga 100%, 99% hingga 100%, –167% hingga 100%, –467% hingga 89%, dan –200% hingga 100%, masing-masing. FECRT untuk separuh dos IVM, dos separuh ABZ, dos penuh ABZ menunjukkan bahawa *H. contortus* mempunyai daya tahan terhadap separuh dos IVM dan ABZ. Dos penuh IVM berkesan terhadap *H. contortus*. Rawatan kombinasi lebih berkesan terhadap *H. contortus* berbanding menggunakan ABZ sahaja.

Kata kunci: Ivermectin, Albendazole, *Haemonchus contortus*, Jawa Barat Indonesia

Abstract: Administering a half dose of an anthelmintic is a simple method for detecting resistance in parasites infesting small ruminants. When a single anthelmintic fails in native sheep from Indonesia, a combination of anthelmintics from different chemical classes with different modes of action are administered as an alternative parasite-control strategy. This study compared the anthelmintic efficacy of ivermectin (IVM) and albendazole (ABZ) given either separately as a single dose or half dose or co-administered to sheep naturally infected with *Haemonchus contortus*. Twelve sheep from Bogor, West Java, Indonesia were divided into the following six treatment groups: half-dose IVM, full-dose IVM, half-dose ABZ, full-dose ABZ, combined IVM + ABZ, and control. The treatment efficacy was determined using the faecal egg count reduction test (FECRT) at day 0 (pre-treatment) and post-treatment at days 7, 14, 21, 28, 35, and 42. The efficacies of half-dose IVM, full-dose IVM, half-dose ABZ, full-dose ABZ, and the combination treatment ranged from –1900% to 100%, 99% to 100%, –167% to 100%, –467% to 89%, and –200% to 100%, respectively. The FECRT for the half-dose IVM, half-dose ABZ, full-dose ABZ showed that

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H. contortus is resistant to half-dose IVM and ABZ. Full-dose IVM was effective against *H. contortus.* The combined treatment was more effective against *H. contortus* than ABZ alone.

Keywords: Ivermectin, Albendazole, *Haemonchus contortus,* West Java Indonesia

INTRODUCTION

In the tropics, gastrointestinal nematodes are a major problem in small ruminants, and they cause disease, death, and decreased production of milk, meat, and wool (Bekele *et al.* 1992; Zainalabidin *et al.* 2014). The barber pole worm, *Haemonchus contortus,* causes haemonchosis, which results in anaemia and digestive disorders. The adult worms live free in the abomasum of the host and attack the mucosa by piercing with their buccal lancets to suck the blood. Female worms produce eggs that are excreted in the faeces into the environment, and the larvae orally infect the host as the ruminants feed on grass (Monnig 1950).

In small ruminants, gastrointestinal nematodes can generally be controlled using broad-spectrum anthelmintics. Widely available commercial anthelmintics commonly used by farmers include macrocyclic lactones (avermectin [AVM] and milbemycins [MLs]), benzimidazole (BZD), and imidazothiazoles (levamisole [LEV] and hydropyrimidines [pyrantel/morantel]). Ivermectin (IVM) is a macrocyclic lactone with broad activity against gastrointestinal nematodes (Egerton *et al.* 1979) and ectoparasites (Campbell *et al.* 1983). IVM acts by binding the α-subunit of glutamate-gated chloride channel receptors (GluCl) in nerve synapses (Wolstenholme 2011), which inhibits nematode feeding, fecundity, and motility (Yates *et al.* 2003). Albendazole (ABZ) is a BZD with a methyl carbamate group that is effective against lung worms (McKellar & Scott 1990), gastrointestinal nematodes, tapeworms, and liver flukes (Campbell 1990). BZD acts by binding to β-tubulin, which inhibits dimerisation with α-tubulin during microtubule formation in nematode cells (Lacey 1990; Wolstenholme 2011).

The intensive use of anthelmintics has led to the development of anthelmintic resistance in small ruminants (Kaplan 2004; Wolstenholme *et al.* 2004). Resistance is considered present when a portion of a population is able to tolerate doses of a compound that are effective against other populations of the same species (Prichard *et al.* 1980). IVM-resistant *H. contortus* has been reported in Australia (Le Jambre 1993), Kenya (Mwamachi *et al*. 1995; Waruiru *et al*. 1998), South Africa (van Wyk *et al*. 1989), and Brazil (Echevarria *et al*. 1991; Vieira *et al*. 1992). BZD-resistant *H. contortus* has been reported in Australia (Green *et al.* 1981), Malaysia (Rahman 1994), India (Uppal *et al*. 1992), France (Kerboeuf *et al*. 1988; Hubert *et al*. 1991), Kenya (Mwamachi *et al*. 1995), South Africa (Berger 1975), and Brazil (Echevarria *et al.* 1991). The resistance problem is compounded by the fact that many parasite populations are resistant to more than one class of anthelmintic. It has been proposed that the combined use of anthelmintics might be more effective against gastrointestinal nematodes when a single anthelmintic has failed. In addition, anthelmintic combinations slow

the development of resistance (Wolstenholme *et al*. 2004; Coles 2005; Leathwick *et al*. 2009).

This study compared the anthelmintic efficacy of IVM and ABZ given separately in a single dose and half dose or co-administered to sheep naturally infected with *H. contortus*.

MATERIALS AND METHODS

Animal

Twelve sheep (age 3–4 months, liveweight 13–20 kg) from Bogor, West Java, were studied. The management system was intensive, the sheep were housed colonially, fed hay, and water was provided ad libitum.

Experimental Design

The sheep were divided randomly into six experimental groups (Table 1). Faecal samples were collected directly from the rectums of the sheep at days 0 (pre-treatment) and at days 7, 14, 21, 28, 35, and 42 post-treatment.

Table 1: The anthelmintic treatment.

Formulation	Route of administration	Dose
Control	–	–
Half-dose IVM	Subcutaneous	½ mL/50 kg liveweight
Full-dose IVM	Subcutaneous	1 mL/50 kg liveweight
Half-dose ABZ	Oral	½ mL/5 kg liveweight
Full-dose ABZ	Oral	1 mL/5 kg liveweight
Combined (IVM + ABZ)	Subcutaneous+oral	(½ mL/50 kg + ½ mL/5 kg) liveweight

Faecal Egg Counts (FEC)

The FEC were determined by a modified McMaster technique that is accurate to 50 eggs per gram. The total number of *H. contortus* eggs counted in two chambers of McMaster slide was multiplied by 50 to obtain the number of egg per gram (epg) of faeces. The FEC were plotted in curves to calculate the *p*-value of the regression. The identification of *H. contortus* eggs was based on the size, shape, and development stage of the eggs (Foreyt 2001).

Anthelmintic

The anthelmintics that were used for treatment were IVM (Ivomec Super, Merial, Brazil) and ABZ (Kalbazen®-SG-Albendazole 19 mg/mL, PT. Kalbe Farma, Bekasi, Indonesia).

Data Analysis

Susceptibility to the various anthelmintic drugs was quantified using the faecal egg counts reduction (FECR) method. The FECR was calculated according to the recommendations of the World Association for the Advancement of Veterinary Parasitology (Coles *et al*. 1992) to evaluate the effectiveness of each

anthelmintic treatment, using the following formula described by Kochapakdee *et al.* (1995) and McKenna (2006):

$$FECR_i\ (\%) = 100 \times [1 - (T_i/T_0)]$$

where $FECR_i$ is FECR on days i, T_i is the arithmetic mean faecal egg counts after treatment (day 7, 14, 21, 28, 35, and 42), and T_0 is the arithmetic mean of the faecal egg counts before treatment (day 0) in the treated group. Anthelmintic effectiveness was based on the FECR (%) and the lower 95% confidence limits. If the FECR percentage of an anthelmintic treatment was less than 95% and the lower 95% confidence limit for the reduction was less than 90%, resistance was considered to be present. If only one of the two criteria was met, resistance was suspected.

RESULTS

Full-dose IVM completely decreased the number of *H. contortus* eggs on day 7. However, the number of eggs was significantly different and actually increased in the control group and the group that received the full-dose ABZ. The anthelmintic combination decreased the number of eggs until day 35 (Fig. 1).

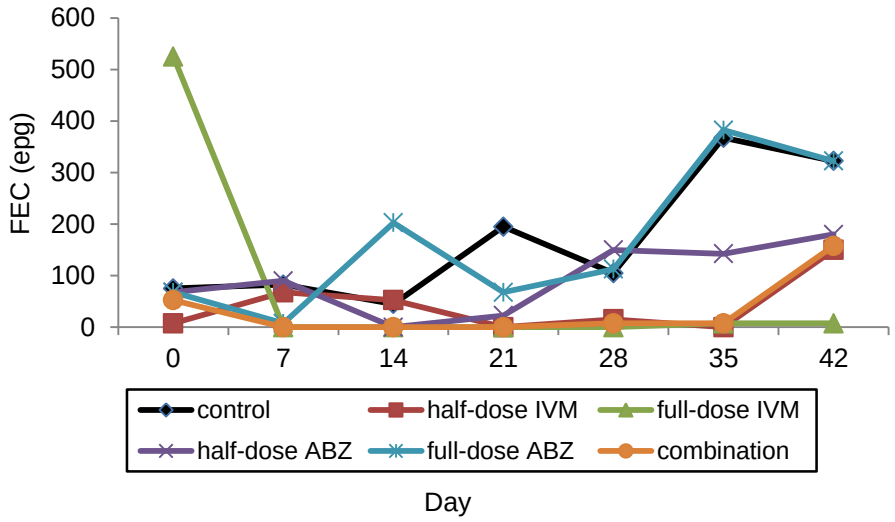

Figure 1: The *H. contortus* faecal egg count (epg) for each treatment, before (day 0) and after (day 7 to 42) treatment.
Note: Control and full-dose ABZ; $p<0.05$.

Table 2 summarises the results of the FECR. The efficacy of half-dose IVM, full-dose IVM, half-dose ABZ, full-dose ABZ, and the combined treatment ranged from –1900% to 100%, 99% to 100%, –167% to 100%, –467% to 89%, and –200% to 100%, respectively. Full-dose IVM had the greatest efficacy at

99%–100%. The low overall percentage reduction showed that *H. contortus* is resistant to IVM and ABZ.

Table 2: FECR (%) and anthelmintic efficacy against *H. contortus* in sheep.

Anthelmintic treatment		Day of treatment						
		Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Control	FEC	150	165	90	390	210	735	645
Half-dose IVM	FECR (%)	0	–800	–600	100	–100	100	–1900
	Upper 95% CL		54	64	100	90	100	–73
	Lower 95% CL		0	0	100	0	100	0
	Drug effectiveness		Resistant	Resistant	Susceptible	Resistant	Susceptible	Resistant
Full-dose IVM	FECR (%)	0	100	100	100	100	99	99
	Upper 95% CL		100	100	100	100	100	100
	Lower 95% CL		100	100	100	100	74	74
	Drug effectiveness		Susceptible	Susceptible	Susceptible	Susceptible	Suspected	Suspected
Half-dose ABZ	FECR (%)	0	–33	100	67	–122	–111	–167
	Upper 95% CL		88	100	97	31	61	32
	Lower 95% CL		0	100	0	0	0	0
	Drug effectiveness		Resistant	Susceptible	Resistant	Resistant	Resistant	Resistant
Full-dose ABZ	FECR (%)	0	89	–200	0	–67	–467	–378
	Upper 95% CL		99	60	91	70	–39	29
	Lower 95% CL		0	0	0	0	0	0
	Drug effectiveness		Resistant	Resistant	Resistant	Resistant	Resistant	Resistant
Combination	FECR (%)	0	100	100	100	86	86	–200
	Upper 95% CL		100	100	100	99	99	–16
	Lower 95% CL		100	100	100	0	0	0
	Drug effectiveness		Susceptible	Susceptible	Susceptible	Resistant	Resistant	Resistant

Notes: FEC = faecal egg counts; FECR = faecal egg count reduction; IVM = ivermectin; ABZ = albendazole; Combination = half-dose ivermectin + half-dose albendazole; CL = confidence limit.

DISCUSSION

Faecal Egg Counts (FEC)

The FEC from each group prior to treatment (day 0) and after treatment (day 7 to 42) are shown in Figure 1. Based on the *p*-value, the significant treatments were the control and full-dose ABZ groups. The control group demonstrated an increase in the number of *H. contortus* eggs that was significant ($p<0.05$). The egg counts increased on days 21 and 35 in the controls because it takes approximately 18–21 days for *H. contortus* larvae to mature and produce eggs (Monnig 1950). Adult female worms can lay an average of 6.582 eggs per day (Coyne *et al.* 1991). By day 14, the control treatment had decreased the number of *H. contortus* eggs. According to Dobson *et al.* (2012), counts of untreated control animals may decrease because of density-dependent constraints on fecundity that are exacerbated by any incoming infection in the period between the pre- and post-treatment counts.

Full-dose ABZ treatment increased the number of *H. contortus* eggs to a level that was significant ($p<0.05$). Cezar *et al.* (2010) showed that a full-dose ABZ treatment increased the number of *H. contortus* eggs by day 12.

Although the response to the full-dose IVM treatment was non-significant, Figure 1 shows that the egg excretion dropped to 0 on day 7 after the administration of full-dose IVM. This result is in agreement with research from Yacob *et al.* (2009) that showed that IVM decreased the egg count to 0 on day 7 until day 21. Other studies have shown that IVM treatment decreased the

number of *H. contortus* eggs on days 5 (McKenna & Watson 1987), 10 (Borgsteede 1993), and 14 (Gogolewski *et al.* 1995).

Faecal Egg Count Reduction Test (FECRT)

Giving half the dose of an anthelmintic is recommended as a simple method for the early detection of resistance (Hughes *et al.* 2005). According to Smith *et al.* (1999), when given at below the recommended dose, the anthelmintic has a shorter half-life. The parasite death rate due to the drug is seen as an instantaneous decrease with the administration of an anthelmintic. On days 7 and 14, the IVM status was resistant, but by day 21, the anthelmintic status became susceptible. Some important factors to be considered in the diagnosis of anthelmintic resistance and the interpretation of results are the route of administration and pharmacokinetic behaviour (Canga *et al.* 2009), host nutrition (Coop & Kyriazakis 2001), and the host immune system and age (Lanusse & Prichard 1993). Subcutaneous administration delays the absorption of IVM from the injection site, resulting in the prolonged presence of the drug in the bloodstream (Canga *et al.* 2009). Depending on the host nutrition, protein content affects the development rate of immunity against parasitic infections, according to Gibson (1983). Protein deficiency causes damage to T-lymphocytes (Beisel 1982). As demonstrated by Gill *et al.* (1993), T-lymphocytes play an important role in combatting haemonchosis in sheep. Sheep under the age of 6 months have very low protection from gastrointestinal nematodes (Lloyd & Soulsby 1987). The half-dose of ABZ was not effective against *H. contortus.* The activity of ABZ depends on the ability of the drug to reach and sustain sufficient concentrations at the site of infection (Lanusse & Prichard 1993).

The full-dose IVM treatment is very effective against gastrointestinal nematodes that are resistant to ABZ, including *H. contortus* (George *et al.* 2011). The efficacy of a drug is also associated with the route of administration. The subcutaneous injection of IVM results in higher plasma IVM concentrations for a longer duration (Alvinerie *et al.* 1998). IVM paralyses the neuromuscular system in the target tissue by increasing the permeability of the plasma membrane to chloride ions (Cl^-). This causes hyperpolarisation and inhibits pharyngeal pumping, feeding, parasite spawning, and muscle motility. The pharynx is a muscular digestive organ that acts in nutrient ingestion and excretion and regulates turgor pressure in the parasite. Paralysis of the pharynx reduces the energy reserves of the parasites (Sangster & Gill 1999) and inhibits feeding by blocking pharyngeal pumping (Geary *et al.* 1993). Paralysis of the uterine muscles in female worms can suppress egg production and the release of eggs that are already present in the uterus. In addition, IVM can sterilise female nematodes in several hosts without killing them (Coles 2005). Le Jambre (1993) reported that IVM suppressed the fecundity of female *H. contortus*. IVM paralyses the somatic muscles in the parasite mid-body, reducing parasite motility and facilitating its expulsion from host intestinal tract (Sangster & Gill 1999).

In contrast, full-dose ABZ was less effective against *H. contortus.* George *et al.* (2011) also reported the low efficacy of ABZ. The mechanism of resistance involves a reduction in the binding affinity of ABZ to tubulin (Sangster *et al.* 2002) due to a mutation in β-tubulin (Kohler 2001). In *H. contortus,* selection for

resistance is enhanced by the high biotic potential. Their fecundity can enable small populations of resistant worms to become large populations in a short amount of time, especially if the climate is favourable for the free-living stages (Craig 1993). In this study, the farmer used ABZ as worm therapeutics for several years. Using the same class of drugs for several years (Coles 2005) ensures that the worms that survive treatment will have a greater chance than susceptible worms to contribute to the next generation.

In this study, the combined treatment with IVM and ABZ was effective against *H. contortus* from days 7 to 21; then, resistance was seen on days 28 to 42, suggesting that *H. contortus* is cross-resistant to the combination treatment. According to Prichard *et al.* (1980), cross-resistance occurs when a population can fight anthelmintics in different chemical groups that have different modes of action. Miller and Craig (1996) reported that the combination of IVM and ABZ was more effective against *H. contortus* than either given alone. Multiple-drug resistance in *H. contortus* has also been reported (Traversa *et al.* 2007; Cezar *et al.* 2010).

CONCLUSION

The percentage reductions in the faecal egg count in the half-dose IVM, half-dose ABZ, and full-dose ABZ groups showed that *H. contortus* is resistant to half-dose IVM and ABZ. The full-dose IVM treatment was 99%–100%, effective against *H. contortus.* The combined treatment was more effective against *H. contortus* than ABZ alone.

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