Development of a resistance management strategy for ixodid ticks (Acari: Ixodidae) infesting livestock from market available acaricides in southern Ghana

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Abstract

The ixodid ticks (Acari: Ixodidae) are the most important ectoparasites infesting livestock in Ghana, causing direct damage to the animals and spreading diseases. The use of acaricides remains the main method for controlling ticks in Ghana. A recent study in Ghana concluded that using a wide variety of acaricides to control ticks on livestock was dangerous as it could lead to resistance in ticks. While it was observed that acaricides of same chemistry were alternated for tick control. These events indicated that in Ghana there is a lack of knowledge on the importance of and how to exploit variety of acaricides to manage tick resistance when cross-resistance patterns have not yet been established. This paper investigated the variety of acaricides on the market for tick conrtol in Accra, Tema and Kasoa in southern Ghana. The acaricides on the market were then used to develop a strategy for managing acaricide-resistance in ticks on livestock. The variety of market acaricides were determined by surveying veterinary pharmacies. Twenty (20) acaricidal products with 8 active ingredients of 4 chemistries were encountered in the study. The chemical groups were amidines, macrocyclic lactones, organophosphates and pyrethroids. The strategy developed for managing resistance in ticks with the acaricidal products on the market was based on mode of action of the active ingredients. The strategy requires the rotaional use of the acaricidal products in ways that reduces the selection pressure of active ingredients of same chemistry on the target-site in tick populations and as a result retard resistance development.

Introduction

Ticks (Acari: Ixodidae, Argasidae and Nuttalliellidae) (Horak *et al*., 2002) are the most economically important ectoparasites of global livestock production (Bowman *et al*., 2004). They act as vectors of a broad range of pathogens of domestic animals (Jongejan and Uilenberg, 2004). Due to their feeding behaviour, ticks are also responsible for causing direct damage, which include tick toxicosis, abscesses due to secondary bacterial infection, lameness, loss of teats and diminish value of skins and hides (Jongejan and Uilenberg, 2004). The ixodid ticks are the most important ticks in Ghana (Walker and Koney, 1999). Ixodid ticks that have been implicated to infest domestic ruminants in Ghana include *Amblyomma variegatum* (Fabricius), *Rhipicephalus (Boophilus) decoloratus* (Koch), *R. senegalensis* Koch, *R. annulatus* (Say) and *Hyalomma marginatum rufipes* (Koch) (Walker and Koney, 1999). Diseases of economic importance of domestic ruminants associated with the ticks in Ghana include dermatophilosis, heartwater (cowdriosis), anaplasmosis and babesiosis (Morrow *et al.*, 1993; Bell-Sakyi *et al.*, 1996; Bell-Sakyi *et al.*, 2004). The direct damage by ticks and the diseases associated with them lead to significant losses in cattle production in Ghana if left uncontrolled (Koney, 1995). Morrow *et al.* (1993) demonstrated that regular acaricidal control of ticks also controlled associated diseases, while Koney (1995) noted that a break in the regular acaricidal control of ticks caused an outbreak of tick associated diseases in Ghana. Thus, control of ticks with acaricides has been the main method for protecting the cattle industry in Ghana against the negative impact of ticks and tick-associated diseases (Awumbila and Bokuma, 1994; Awumbila, 1996). However, reliance on acaricides to control ticks eventually results in the development of resistance in the ticks. When ticks develop acaricide-resistance, otherwise useful acaricides are rendered useless resulting in tick control failures, which lead to tick and tick-associated disease outbreaks. Resistance to acaricides in ticks on livestock also increases the risk of acaricide residues in meat and milk, in addition to environmental contamination. Although acaricide-resistance in ticks has been detected in Ghana (Turkson & Botchey, 1999; Koney and Nipah, 2000) and acaricides continue to be widely used for tick control (Addah *et al.*, 2009; Nkegbe *et al.*, 2013), effective strategies for managing tick resistance to acaricides are lacking.

In a study into acaricide use by farmers in Accra and Tema in southern Ghana, Nkegbe *et al.* (2013) encountered sixteen (16) acaricidal products which contained active ingredients of 3 chemistries. Nkegbe *et al.* (2013) concluded that there was a high level of variety in the acaricides being used by farmers which was dangerous as it could lead to resistance in ticks. The conclusion reached by Nkegbe *et al.* (2013) is misleading because the use of acaricides from 3 chemical groups does not indicate a high level of variety, while variety is actually good for resistance management (Ninsin, 2016). The conclusion by Nkegbe *et al.* (2013) is of major concern as it could lead to the use of a low variety of acaricides which would exacerbate resistance in ticks. We also observed that on a dairy farm in Accra belonging to the Ministry of Agriculture, when Cypertop®, a product that contains a mixture of cypermethrin (pyrethroid) and chlorpyrifos (organophosphate [OP]) could no longer control ticks on cattle, the product was replaced with Vetancid® Max, which contains a mixture of cypermethrin and trichlorfon (OP). When Vetancid® Max could also not control the ticks it was replaced with Ectocyp®, a product that contains cypermethrin, which also failed and resulted in the desperate use of acaricide dilutions that was not recommended. Although different acaricidal products were alternated to control the ticks on the farm, the acaricides were not different as the products had the same cypermethrin active ingredient, while chlorpyrifos and trichlorfon are OPs. Thus, the alternation caused a sustained and increased selection pressure on the ticks from pyrethroid and OP acaricides simultaneously. Such intense selection pressure accelerates the development of multiple-resistance to pyrethroids and OPs in ticks or aggravates an already existing resistance leading to tick control failures and risking meat and milk safety and environmental quality.

It is evident from the above that in Ghana knowledge on the importance and use of a variety of acaricides of different chemistries to manage resistance development in ticks on livestock when cross-resistance studies have not been done is lacking. Thus, this study determined the variety of acaricides on the market for controlling ticks on livestock in southern Ghana. The acaricides were then used to develop a strategy for managing resistance development in ticks on livestock.

Materials and methods

Determination of market available acaricides for tick control

The Food and Drugs Authority (FDA) is mandated by the Food and Drugs Law, 1992 (PNDCL 305B), the Food and Drugs Amendment Act, 1996 (Act 523) and the Public Health Act, 2012 (Act 851) to regulate veterinary pharmaceuticals in Ghana, including acaricides for controlling ticks on livestock. The FDA was therefore contacted for registered acaricides. However, several of the known acaricides used to control ticks in Ghana were not on the FDA list. Thus, veterinary pharmacies in the Accra-Tema metropolitan area and Kasoa in the Greater Accra Region and Central Region of Ghana, respectively, were sampled for acaricides on sale. The snowball sampling method was used to locate veterinary pharmacies. Known veterinary pharmacies were contacted for the names and locations of other pharmacies in the study area. The snowballing was continued to increase the number of veterinary pharmacies for the study. Due to the low numbers of veterinary pharmacies, the sampling method yielded a dozen pharmacies. Thus, all pharmacies encountered were included in the investigation for data collection. Data collected from each veterinary pharmacy on acaricides from product labels were product name, product type, active ingredient, chemical group, concentration of active ingredient and formulation. The data were analyzed to determine the variety of acaricides on the market, which were then used to develop a strategy for managing tick resistance in Ghana.

Development of strategy for tick control with market acaricides

The strategy for tick control with the market acaricides was developed by identifying the mode of action (MoA) of active ingredients of the acaricidal products using the MoA classification scheme by Insecticide Resistance Action Committee [IRAC] (2016). Acaricidal products were grouped based on the MoA for rotation according to Ninsin (2016) in order to reduce the selection pressure of active ingredients of same chemistry on the target-site in tick populations.

Results and discussion

A total of 20 acaricidal products for the control of ticks on livestock were found on the market (Tables 1 and 2). Although all the acaricidal products observed in the study had labels indicating that they had been formulated and recommended for the control of ticks on livestock, only 30 per cent (6 out of 20) of the products had been registered by the FDA. The acaricidal products had 8 active ingredients of 4 chemistries (Tables 1 and 2). Two of the acaricidal products were mixtures (Table

TABLE 1

Products with single active ingredient on the Ghanaian market for controlling ticks on livestock

Product name	*Product type*	*Active ingredient*	*Chemical group*	*Concentration of active ingredient (g/l)*	*Formulation*
Amiraz	Acaricide	Amitraz	Amidine	200 g/l	Emulsifiable concentrate
Amitix	Acaricide	Amitraz	Amidine	125 g/l	Emulsifiable concentrate
Intraz	Acaricide	Amitraz	Amidine	125 g/l	Emulsifiable concentrate
Milbitraz spray dip[a]	Acaricide	Amitraz	Amidine	125 g/l	Emulsifiable concentrate
Taktic	Acaricide	Amitraz	Amidine	125 g/l	Emulsifiable concentrate
Triatix	Acaricide	Amitraz	Amidine	125 g/l	Emulsifiable concentrate
Ashiver[a]	Endectocide	Ivermectin	Macrocyclic lactone	10 mg/ml	Injectable solution
Dufamec	Endectocide	Ivermectin	Macrocyclic lactone	10.2 mg/ml	Drench
Iverm[a]	Endectocide	Ivermectin	Macrocyclic lactone	10 mg/ml	Injectable solution
Kelamectin[a]	Endectocide	Ivermectin	Macrocyclic lactone	10 mg/ml	Injectable solution
Kepromec	Endectocide	Ivermectin	Macrocyclic lactone	10 mg/ml	Oral suspension
Unimec[a]	Endectocide	Ivermectin	Macrocyclic lactone	10 mg/ml	Oral suspension
Conti-zol "5"	Acaricide	Diazinon	Organophosphate	50 g/l	Emulsifiable concentrate
Diason	Acaricide	Diazinon	Organophosphate	600 g/l	Emulsifiable concentrate
Bayticol	Acaricide	Flumethrin	Pyrethroid	20 g/l	Emulsifiable concentrate
Drastic Deadline[a]	Acaricide	Flumethrin	Pyrethroid	10 g/l	Pour-on
G-Tocyp	Acaricide	Cypermethrin	Pyrethroid	100 g/l	Emulsifiable concentrate
Vectocid	Acaricide	Deltamethrin	Pyrethroid	50 g/l	Emulsifiable concentrate

[a] Products registered as at 7th May 2013 by Food and Drugs Authority, Ghana

TABLE 2

Products with mixture of active ingredients on the Ghanaian market for controlling ticks on livestock

Product name	*Product type*	*Active ingredient*	*Chemical group*	*Concentration of active ingredient (g/l)*	*Formulation*
Cypertop	Acaricide	Cypermethrin	Pyrethroid	50 g/l	Pour-on
		Chlorpyrifos	Organophosphate	70 g/l	
		Piperonyl butoxide	Synergist	50 g/l	
		Citronella	Repellent	5 g/l	
Vetancid® Max	Acaricide	Cypermethrin	Pyrethroid	50 g/l	Pour-on
		Trichlorfon	Organophosphate	100 g/l	

2). Six products contained the active ingredient ivermectin (the avermectins) which belongs to the macrocyclic lactone (ML) group. Ivermectin has systemic activity and are endectocides. Acaricidal products that contain ivermectin are therefore formulated to be administered orally or as injection (Table 1). On the other hand, products with amidine, OP and pyrethroid active ingredients have contact activity and are only acaricidal. Acaricidal products with amidine, pyrethroid or OP are therefore formulated as either pour-on for direct application to the backline of livestock or as emulsifiable concentrate (EC) for spraying and dipping (Tables 1 and 2).

The 20 acaricidal products on the market do not indicate a wide variety of acaricides as they act on only 4 target sites. The amidine acaricides are octopamine receptor agonists which activate octopamine receptors leading to hyperexcitation (IRAC, 2016). The MLs are chloride channel activators and they allosterically activate the glutamate-gated chloride channels, causing paralysis (IRAC, 2016). The OP acaricides inhibit acetylcholinesterase, causing hyperexcitation (IRAC, 2016), while the pyrethroids, as sodium channel modulators, keep sodium channels open, causing hyperexcitation and, in some cases, nerve block (IRAC, 2016).

Due to a common MoA of all acaricides of same chemistry, when ticks develop resistance to one active ingredient in a chemical group, the resistance extends to all other active ingredients in the group as a result of insensitive target-site (Ninsin, 2016). For this reason the rational use of acaricides with different MoA helps retard resistance development in ticks. The rotational use of acaricides with different MoA to control ticks decreases the selection pressure from an active ingredient on its target-site thereby retarding resistance development caused by insensitive target-site (Ninsin, 2016). Thus, the strategy developed for controlling ticks on livestock with the market acaricides as presented in Fig. 1 and 2, involves the rotational use of acaricidal products containing active ingredients with different MoAs.

To manage acaricide resistance development with acaricidal products on the market that contain single active ingredients (Table 1), the acaricides should be used for tick control in a rotation as outlined in the example below and in Fig. 1:

- Use an acaricidal product containing an active ingredient that belongs to a chemical group (example, ML) which is different from the last used active ingredient's chemical group (example, amidine).
- The next acaricide application should be with a product that contains an active ingredient which belongs to a chemical group (example, OP) other than the two previously used chemical groups (i.e., amidine and ML).
- For the next application, use a product with active ingredient belonging to a chemical group (i.e., pyrethroid) different from the three previously used chemical groups (i.e., amidine, ML and OP).

Thus, all four acaricidal groups (amidines, MLs, OPs and pyrethroids) on the market

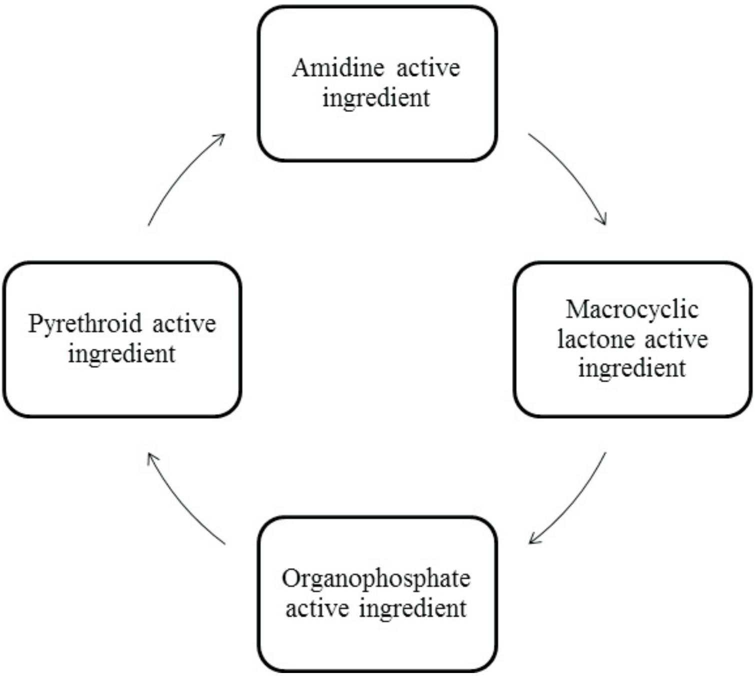

Fig. 1. Model of rotation of market available acaricidal products with single active ingredient listed in Table 1

would have been used once in a rotation before using a product with an active ingredient from the chemical group that was first used for tick control, i.e., amidine in the example, to start the rotation all over again (Fig. 1).

The products with mixture of active ingredients on the market both contain pyrethroids and OPs (Table 2). Mixture of active ingredients exposes tick populations to selection pressure from multiple active ingredients at the same time and could lead to multiple-resistance. Thus, if mixtures are to be used for tick control, they also have to be used in a rotation in order not to risk the development of multiple-resistance in ticks. Table 2 shows that the acaricidal product, Cypertop®, contains in addition to the active ingredients, the synergist piperonyl butoxide (PBO) and the repellent, citronella. The PBO is an inhibitor of cytochrome P-450 monooxygenases (P450s) (Keserü *et al*., 1999) and, to some extent, esterases (Young *et al*., 2002). Esterases and P450s are important metabolic enzyme systems involved in resistance that could confer cross-resistance between different chemical groups. Mixing an active ingredient with PBO has been shown as a practical means to enhance the efficacy of the active ingredient in a pest that is resistant as a result of metabolic resistance (Ninsin and Tanaka, 2005). The addition of PBO to Cypertop® is therefore to suppress the P450s and esterases to enhance the efficacy of cypermethrin and chlorpyrifos in controlling the ticks. Notwithstanding the usefulness of PBO in Cypertop®, uncontrolled exposure of ticks to Cypertop® could still result in the simultaneous development of target-site resistance to the active ingredients in the product. In order to prevent the development of multiple-resistance, when any of the acaricidal products with mixture of active ingredients in Table 2 is used once for tick control, it has to be considered that the slots for OPs and pyrethroids in the rotation of acaricides in Fig. 1 has been used. Thus, the next acaricide application should be with a product containing an amidine as depicted in Fig. 2.

During the rotation, acaricides of same chemistry must be applied for a generation of the target tick before applying acaricides of different chemistry in order to retard the accumulation of resistant individuals in the population (Ninsin, 2016). It is also worth noting that since ivermectin is an endectocide, it is important to plan its use to coincide with time to control both endoparasites and ectoparasites. This is because using the drug to control the endoparasites or ectoparasites at different times would increase the selection pressure of the drug and result in resistance in both endoparasites and ectoparasites.

The survey indicated that majority of the acaricidal products with same active ingredient and same formulation had comparable concentrations of active ingredient. However, Amiraz® contained 200 mg/l amitraz while other products with amitraz contained 125 mg/l of active ingredient. Additionally, Contizol "5"® and Diason® contained 50 mg/l and 600 mg/l diazinon, respectively. Thus, when deciding between the acaricidal products with same active ingredient and formulation but different concentrations of active ingredient, it is important to use the product that has been used previously for

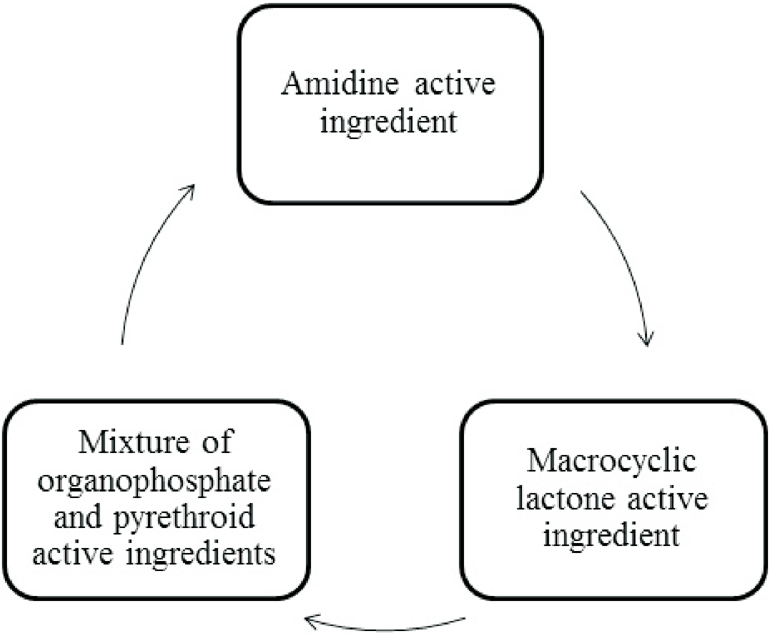

Fig. 2. Model of rotation of market available acaricidal products with mixture of organophosphate and pyrethroid active ingredients listed in Table 2 with products containing amidine or macrocyclic lactone active ingredient listed in Table 1.

tick control. If an active ingredient is being used for the first time, then the product with the lower concentration would have to be chosen for incorporation into the rotation in order not to unnecessarily increase selection pressure.

Due to the possibility of cross-resistance between active ingredients of different chemistries (Ninsin, 2004a; Ninsin, 2004b) caused by metabolic resistance (Ninsin and Tanaka, 2005), the success of a rotation with acaricides from few chemical groups could be undermined. Therefore, to increase the chance of success of a rotation, it is prudent to increase the variety of acaricides for tick control by increasing the chemical groups of acaricides. According to Nkegbe *et al.* (2013), the acaricidal products used by farmers to control ticks on livestock were amidines, OPs and pyrethroids. Adding the MLs found on the market in this study to the amidine, OP and pyrethroid acaricides for rotation as shown in Figures 1 and 2 to control ticks on livestock would add variety to the MoA of acaricides and retard resistance development.

There are other acaricides of different chemistries and with different MoAs for controlling ticks on livestock that are not available on the market in Ghana. When these acaricides become available in Ghana, they would have to be incorporated into the rotation model (Fig. 1) to retard resistance to the active ingredients. Similarly, when acaricidal products with mixtures of active ingredients that are different from those encountered in the survey become available for tick control in Ghana, they would also have to be incorporated into the rotation model for mixtures (Fig. 2) to retard resistance development in ticks. Importers of acaricidal products for the Ghanaian market are encouraged to comply with the regulatory requirement on the registration of acaricides, so that all active ingredients for control of ticks on livestock would be known and properly managed to prevent resistance development.

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