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REVIEW ARTICLE

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Drugs for External Parasites, their use and Problems in Gondar University Veterinary Clinic

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ABSTRACT

Ectoparasites are major problems of the animal husbandry system that causes production losses by feeding on animal's body tissues and annoying feeding animals. Wounds produced during feeding of parasites are sites of secondary infection. Blood sucking insects also transmit diseases from animal to animal and from animal to humans. accaricides are drugs that act on these ectoparasites. Among these accaricides organophosphates and ivermectine are widely available and are used extensively. The study was conducted in the veterinary clinic of university of Gonder, Gonder, Ethiopia with the objectives of assessing proper usage of accaricides for the treatment of ectoparasite infestations during the last five years and their problems hence indicating scientific ways to address the problems and getting the best effects. Retrospective method of study design was conducted and all case books recorded for the last five years were assessed. Only cases of ectoparasite infestation was considered as a potential data and used for the study.

The result of this study showed that the majority of ectoparasitic infestations were encountered during summer periods where as the level of infestation was minimum during winter periods. 57.7% of cases were treated with ivermectin while diazinon serves as a

choice of treatment for the remaining 42.3% of ectoparasitic cases. Bovines (77.9%) were the most infested species of animals followed by Canines (16.3%) where as equines (1%) were found the least infested species.
Keywords: Ectoparasites, Accaricides, Gonder, Ivermectine and Diazinon.

INTRODUCTION

External parasites are the most serious impact since they feed on body tissues such as blood, skin and hair. The wounds and skin irritation produced by these parasites often result in discomfort and irritation for the animal. More significant, however, is that any blood-sucking arthropod may transmit diseases from infected animals to healthy ones. In addition, arthropod pests also may reduce weight gains, causes losses in milk and meat production, produce general weakness, cause mange and severe dermatitis, and create sites for secondary invasion of disease organisms. In general, infected livestock cannot be healthy or efficiently managed to realize optimum production levels (E. P. and G. R. Mullen, 2002).
Parasitic infections are of paramount economic importance in small ruminants and result in lowered resistance, loss of production and even mortality (Singla, 1995). Among these infections skin diseases caused by lice, sheepkeds, fleas, ticks and mange mites are among the major diseases of small ruminants and causes serious economic loss due to; mortality, decreased production and reproduction as well as downgrading and rejection of skin. Moreover, ectoprasites are very important vectors for numerous microbial infectious diseases affecting livestock (Radostits et al., 2007). Some 35% of sheep and 56% of goat skin rejections in Ethiopia are due to affection by ectoparasites. The figures portray seriousness of negative economic impact posed by ectoparasites on livelihoods, the tanning industry and the national economy in the country (Chanie et al., 2010). Therefore, to overcome these problems many preparations are available to treat, prevent and control flea, tick infestations, mites (mange), lice, fly bites and other external parasites. They vary in their effectiveness, length of activity, species on which they can be used. An ectoparasiticide is an anti parasitic drug used in the treatment of ectoparasites. These drugs are used to kill the parasite that lives on the animal body surface (Taylor MA, 2001). Anti parasitic treatment has evolved to the concept of prevention of ecto-parasite infestations through the introduction of formulations providing long lasting activity. At the same time, ease of use has been improved with the development of anti parasitic drugs providing control of both external and internal parasites (E. Guaguère, F. Beugnet, 2008). control of external parasites in the recent past has relied heavily on the use of effective chemicals, such as the arsenicals ,chlorinated hydro carbons, organophosphates, carbamates, formamidines, pyrethyroides, macrocyclic lactone and more recently the insect growth regulators(IGRs). Success in the chemicals use has depended on the organism's susceptibility to them, management, their application and availability (Geary and Thompson, 2003).

Therefore, the objectives of this study are

- To describe briefly drugs for external parasites their use and problems
- To reduce the side effect of drugs
- To improve animal health status
- To improve the quality of animal hide

LITERATURE REVIEW

Chemotherapeutic agents for the treatment of ectoparasites

Ivermectin

Ivermectin is a medication that is effective against many types of parasites *(*Elsevier Health Sciences, 2015). It first appeared in the late 1970s. Ivermectin, a derivative of avermectin, was a truly revolutionary drug, unprecedented in many ways. It was the world's first endectocide, forerunner of a completely new class of antiparasitic agents, potently active against a wide range of internal and external nematodes and arthropods (Ōmura S., 2008).

Mode of action

Initially, researchers working on the development of ivermectin believed that it blocked neurotransmitters, acting on GABA-gated Cl^- channels, exhibiting potent disruption at GABA receptors in invertebrates and mammals. GABA is recognised as the primary inhibitory neurotransmitter in the somatic neuromuscular system of nematodes. Subsequently, they discovered that it was in fact glutamate-gated Cl^- channels ($GUCl^-$) that were the target of ivermectin and related drugs. This discovery opened up a completely new spectrum of possibilities, as these channels, although playing fundamental roles in nematodes and insects are not accessible in vertebrates (Omura, 2002). Ivermectin, while paralyzing body-wall and pharyngeal muscle in nematodes has no such impact in mammals, as it cannot cross the blood-brain barrier into the mammalian Central Nervous System, where GABA receptors are located (Omura, 2002).

Pharmacodynamics

Ivermectin are macrocyclic lactones derived from the bacterium Streptomyces avermitilis. Ivermectin kills by interfering with nervous system and muscle function, in particular by enhancing inhibitory neurotransmission. The drug binds to glutamate-gated chloride channels (GluCls) in the membranes of invertebrate nerve and muscle cells, causing increased permeability to chloride ions, resulting in cellular hyper-polarization, followed by paralysis and death (Yates DM and Wolstenholme 2004).

Pharmacokinetics

Ivermectin can be given either orally or by injection. It does not readily cross the blood–brain barrier of mammals due to the presence of Permeability glycoprotein. Crossing may still become significant if ivermectin is given at high doses. In contrast to mammals, ivermectin can cross the blood–brain barrier of invertebrates (*Borst P.and Schinkel AH, 1996)*.

Veterinary use

In veterinary medicine ivermectin is used against many intestinal worms (but not tapeworms), most mites, and some lice. Despite this, it is not effective for eliminating ticks, flies, flukes, or fleas. It is effective against larval heartworms, but not against adult heartworms, though it may shorten their lives. The dose of the medicine must be very accurately measured as it is very toxic in over-dosage. It is sometimes administered in combination with other medications to treat a broad spectrum of animal parasites (**Dourmishev AL. et al, 2005).**

Veterinary problem

Its use became widespread in animal health; ivermectin resistance began to appear, at first in small ruminants but also, more significantly in cattle parasites (Kaplan R.M. 2004).

Diazinon

Diazinon is an organophosphate insecticide and acaricide (a chemical which kills mites and ticks), which acts as a contact stomach and respiratory poison. It is used throughout the world to control a wide range of insects and mites. In common with other organophosphates, diazinon's toxic action is achieved by inhibiting acetylcholinesterase, an enzyme essential for normal nerve impulse transmission (WHO, 1998).

Mode of action

Inside living things, diazinon is transformed in to a molecule called diazoxon. Diazinon, and it's more potent metabolite kill insects by interfering with nervous system function, as do all members of the organophoshate chemical family (U.S. Dept. of Health and Human Services, 1996).

Organophosphates attach to AChE and prevent it from destroying acetylcholine, causing overstimulation of the nerves (Ware, G.W. 2000). Mammal and insect nervous systems are similar enough that effects of organophosphates are similar (Reigart, J.R. and J.R. Roberts. 1999). It is worth noting that not all of diazinon's toxicological effects stem from its inhibition of AChE. Diazinon and other organophosphates inhibit numerous enzymes with molecular structures that are similar to AChE. For example, an enzyme involved in the metabolism of the amino acid tryptophan is strongly inhibited by diazinon and diazoxon (Seifert, J. and T. Pewnim, 1992).

Pharmacodynamics

As all organophosphate insecticides, diazinon acts on the nervous system of the parasites (but also of mammals, birds, fish and many organisms) by inhibiting the activity of acetylcholinesterase, an enzyme that hydrolyzes acetylcholine (Ach). Hence, prevent the termination of nerve signals, the neurons remain in constant activity and excitation, massively disturbing the normal movements of the parasites. The bottom line for the parasites is that they are paralyzed and die more or less quickly (parasitipedia.net, 2016).

Pharmacokinetics

Percutaneous absorption (i.e. through the skin) of topically administered diazinon depends on the animal species, the administered dose, and the extension of the treated body surface. As a general rule, only a relatively low amount is absorbed into blood after topical administration. Animals treated topically can ingest diazinon through licking and grooming. Ingested diazinon is vastly absorbed into blood and quickly metabolized. Half-life of ingested diazinon is about 12 hours. In dogs 58% is excreted through urine in the first 24 hours after administration, >85% in the form of various metabolites. One of the main metabolites, diazoxon is an acetylcholinesterase inhibitor substantially more potent (i.e. more toxic) than diazinon itself (parasitipedia.net, 2016).

2.2.5 Veterinary use

As most organophosphates diazinon is used as broad-spectrum insecticide, acaricide and larvicide. It is especially effective against scab and mange mites (*Psoroptes* spp, *Sarcoptes*spp., etc.), flies, fleas, lice, blowfly strike, and insects in general, but less effective against ticks (parasitipedia.net, 2016).

Veterinary problem

Acute intoxication is caused by inhibition of the acetylcholinesterase. As a consequence acetylcholine accumulates in the neuromuscular synapses (including those in skeletal, smooth and cardiac muscles), in the neuroglandular connections, and in the CNS (Central Nervous System). This causes hyper excitation in all the muscarinic and nicotinic cholinergic receptors, which disturbs the normal functioning of the affected organs (parasitipedia.net, 2016).

After accidental ingestion or massive dermal overdose, intoxication follows an acute development. Ingested diazinon is vastly and quickly absorbed into blood. The symptoms appear a few minutes to 2 hours after ingestion, often dramatically. If the patient survives the first 24-48 hours, prognosis is favorable (parasitipedia.net, 2016).

Usually muscarinic symptoms are the first to manifest, followed by hyper excitation of the nicotinic receptors of vegetative ganglions and motor end plates. If the intoxication crosses the blood-brain barrier the CNS becomes hyper excited as well (parasitipedia.net, 2016).

Chronic intoxication in addition to the acute intoxication, some organophosphates can have a delayed neurotoxic effect (so called OPIDN = *organophosphorous ester-induced delayed neuropathy*), which develops 7 to 21 days after exposure to the toxic dose and appears as weakness, ataxia (uncoordinated movements), proprioceptive dysfunctions (disturbed awareness of posture and movements), particularly of the hind legs, and paralysis. It is due to degeneration of the axons (nerve fibers) of central and peripheral nerve cells, which is species-specific. Depending on which particular organophosphate caused the intoxication, OPIDN is irreversible or allows a slow recovery after several weeks (parasitipedia.net, 2016).

Dichlorodiphenyltrichloroethane (DDT)

DDT (dichlorodiphenyltrichloroethane) is a colorless, crystalline, tasteless and almost odorless organochloride known for its insecticidal properties and environmental impacts. DDT has been formulated in multiple forms, including solutions in xylene or petroleum distillates, emulsifiable concentrates, water-wettable powders, granules, aerosols, smoke candles and charges for vaporizers and lotions (World Health Organization, 1989)

History

First synthesized in 1874, DDT's insecticidal action was discovered by the Swiss chemist Paul Hermann Müller in 1939. It was used in the second half of World War II to control malaria and typhus among civilians and troops. After the war, DDT was also used as an agricultural insecticide and its production and use duly increased (World Health Organization, 1979). Müller was awarded the Nobel Prize in Physiology or Medicine "for his discovery of the high efficiency of DDT as a contact poison against several arthropods" in 1948 (NobelPrize.org).

Mechanism of insecticide action

DDT affects the peripheral nerves and brain by slowing Na+ influx and inhibiting K+ outflow. This results in excess intracellular K+ in the neuron, which partially depolarizes the cell. The threshold for another action potential is decreased, resulting in increased firing of the neuron, which leads to spasms and eventual death. Insects with certain mutations in their sodium channel gene are resistant to DDT and similar insecticides. DDT resistance is also conferred by upregulation of genes expressing cytochrome P450 in some insect species as greater quantities of some enzymes of this group accelerate the toxin's metabolism into inactive metabolites (Denholm et al., 2002).

Veterinary problem

Toxic effect

DDT is classified as "moderately toxic" by the US National Toxicology Program (NTP) and "moderately hazardous" by WHO, based on the rat oral LD50 of 113 mg/kg. DDT can be absorbed orally and topically. These compounds are lipid soluble, which makes absorption rapid. After being absorbed it is distribution to the liver, kidney, brain, and any adipose tissue. DDT metabolites may be more toxic than the parent compound (World Health Organization, 2005).

Environmental impact

DDT is a persistent organic pollutant that is readily adsorbed to soils and sediments, which can act both as sinks and as long-term sources of exposure affecting organisms. Depending on conditions, its soil half life can range from 22 days to 30 years. DDT is toxic to a wide range of living organisms, including marine animals such as crayfish, daphnids, sea shrimp and many species of fish. 56 Due to hydrophobic properties, in aquatic ecosystems DDT and its metabolites are absorbed by aquatic organisms and adsorbed on suspended particles. Because of its lipophilic properties, DDT can bioaccumulate, especially in predatory birds. Hence, in the 1970s and 1980s, agricultural use was banned in most developed countries. The Stockholm Convention on Persistent Organic Pollutants, which took effect in 2004, outlawed several persistent organic pollutants, and restricted DDT use to vector control. The Convention was ratified by more than 170 countries (Connell, D., 1999).

Pyrethroids

Synthetic pyrethroids possess high insecticidal efficacy combined with a low toxicity to mammals and a good UV-stability. Galenic formulations are available guaranteeing a long-term effect after a single application (Liebisch, 1986 and Vythilingam, 1993). Pyrethroid insecticides are thus increasingly being used on farm animals to control ectoparasites such as flies, mosquitoes, malophaga and ticks that annoy grazing cattle. However, the extensive use of synthetic pyrethroids on farm animals may lead to unwanted, chronic exposure of humans, other animals, and the environment (Chen, 1991).

History

Natural pyrethrins are extracted from flowers of certain species (e.g. *Pyrethrum*, *Chrysanthemum*) and have insecticidal and repellent properties. After the discovery of the chemical structure of natural pyrethrins in the 1920's, the first synthetic pyrethroid, allethrin, was introduced in the 1950's. It breaks down quickly when exposed to sunlight and is less effective against insects than natural pyrethrins. In the 1960's and early 1970's second-generation pyrethroids were progressively introduced (e.g. tetramethrin and phenothrin). They were 20 to 50 times more potent than allethrin. A third generation followed (e.g. fenvalerate, permethrin) with a better stability against UV-light. The last generation (e.g. cypermethrin, deltamethrin, cyfluthrin, cyhalothrin and flumethrin) was introduced at the end of the 1970's and contributed substantially to the huge success of synthetic pyrethroids in agriculture, animal health and hygiene (parasitipedia.net, 2016).

2.4.2 Mechanism of insecticide action

Pyrethroids are axonic excitoxins, the toxic effects of which are mediated through preventing the closure of the voltage-gated sodium channels in the axonal membranes. The sodium channel is a membrane protein with a hydrophilic interior. This interior is a tiny hole which is shaped precisely to strip away the partially charged water molecules from a sodium ion and create a favorable way for sodium ions to pass through the membrane, enter the axon, and propagate an action potential. When the toxin keeps the channels in their open state, the nerves cannot repolarize, leaving the axonal membrane permanently depolarized, thereby paralyzing the organism (Soderlund, et al, 2002).

Environmental effects

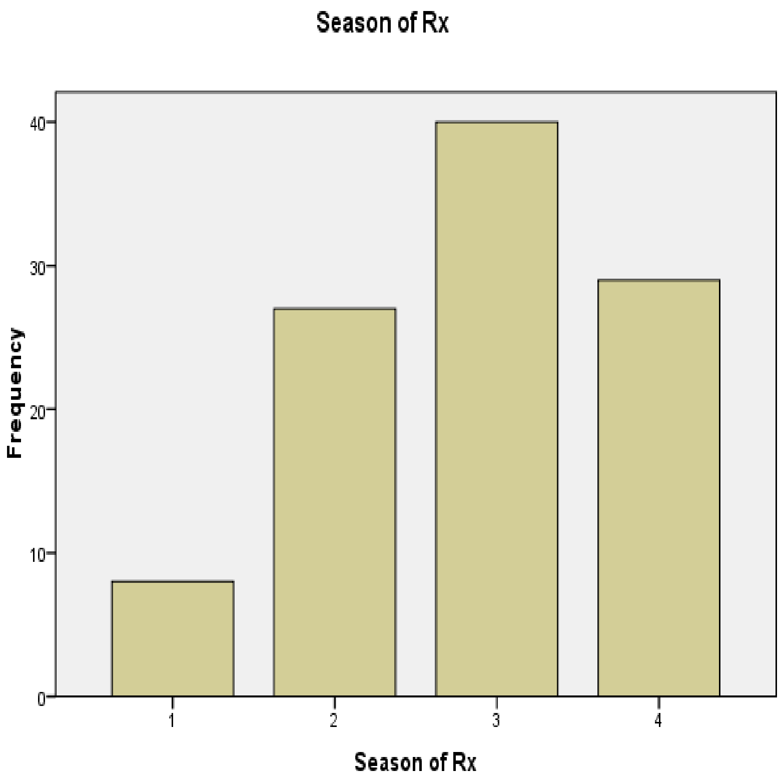
Aside from the fact that they are also toxic to beneficial insects such as bees and dragonflies, pyrethroids are toxic to fish and other aquatic organisms. At extremely small levels, such as 4 parts per trillion, pyrethroids are lethal to mayflies, gadflies, and invertebrates that constitute the base of many aquatic and terrestrial food webs (Zaveri and Mihir, 2010).

Veterinary problem
Pyrethroids became more commonly used against insectes, but resistant populations have now developed (Jerome Goddard & Richard deShazo, 2009*)*.

MATERIAL AND METHODS

Study area

The study was conducted in Gondar town, North Gondar administrative zone of Amhara National Regional State (ANRS). Gondar is located in the North-Western part of Ethiopia, 710 kms North West of Addis Ababa. The study area is found at 12°40'1N longitude and 37°45'1E, latitude with an altitude range of 1802-2200 metres above sea level. The soil type falls into three categories: Heavy black clay soil, loam brown and red soil and sandy loam soil. The ranges of maximum and minimum temperature vary between 22-30.7 and 12.3-17.1°C, respectively. The region receives a bimodal rainfall, the average annual precipitation rate being 1000 mm. The short rains occur during the months March, April and May while the long rains extend from June through September (MOA, 2004).



1- spring
2- winter
3-autumn
4-summer

Figure 1. Season of ectoparasite infestation occurrence.

Method of data collection

Retrospective study

This research was employed retrospective study design in which ectoparaciticides used for the past three years were assessed back. Data was collected from case books recorded for the last three years. All case books recorded for the last three years were reviewed and cases of ectoparasite infestation have been considered for the study.

Data analysis
The data will be analyzed using SPSS version-16 statistical software. Pearson's Chi square test is used to measure statistical significance of results. In order to consider a result to be statistically significant 95% CI and p-value < 0.05 will be taken

RESULT
Season of ectoparacite infestation
The highest level of ectoparasite infestation was encountered during the season when maximum rainfall occurs. Spring and autumn periods with low rainfall are also potential ectoparasite infestation periods. The lowest infestation was recorded during winter when lowest rainfall occurs. Even though a large amount of rain presents in summer, about 55.2% of infestations were treated with diazinon rather than ivermectin. During winter only about 29.6% of infestation cases were treated by spraying diazinon and the remaining 70.4% of cases were recorded as been treated with ivermectin.

Drugs used for the treatment of ectoparasites
Even though a number of paraciticide drugs are available inside the clinic and in the market commercially, only two types of drugs namely ivermectin and diazinon are used extensively.

Table 1. Drugs used during the treatment of ectoparasites.

	Frequency	Percent
Ivermectin	60	57.7
Diazinon	44	41.3

Routes the drugs administered
Subcutaneous and topical routs were recorded to be used commonly for the application of ectoparasiticide drugs. Unlikely intramuscular route was also found recorded as a route of administration of ivermectin but with small frequency.

Table 2. Routes the drugs administered.

			Drugs used	
Route of administration	Frequency	percent	ivermectin	diazinon
Subcutaneously	57	54.8	95	0
Topically	44	42.3	0	100
Intramuscularly	3	2.9	5	0

Types of ectoparasites identified and treatment options undertaken
Different groups of ectoparasites have been found recorded as been diagnosed and treated in the veterinary clinic of university of Gondar during the last five years. These include ticks, fleas, lice and mange mites. Ticks (34.6%) account the larger portion of external parasites identified followed by mange mites (17.3%). Infestation from flea (16.3%) was also occurred in considerable level and the same level of infestation (16.3%) was also recorded from a combination of different groups of ectoparasites at the same time followed by lice infestation (10.6%). Infestation by a combination of two different groups of ectoparasites like lice and tick 92.9%), flea and tick (1%) and mite and tick (1%) also identified in small level.

The majority of tick (58.3%) infestations was treated by spraying an acaricide diazinon and the remaining 41.7% of tick infestation cases were treated with an endectoparaciticide ivermectin. 41.2% of fleas, 94.4% of mites and 54.5% of lice infestation cases were treated by injecting ivermectin where as the remaining fraction of these cases were treated with diazinon.

Species of animals infested and drugs of choice administered
Bovines (77.9%) were the most infested species of animals where as equines (1%) were the least infested species according to the data recorded for the last five years in the veterinary clinic of university of Gondar. Canines (16.3%) were found the second most infested species followed by ovines (4.8%). 88.2% of infested canines were treated with ivermectin and the remaining 11.8% were treated by spraying with diazinon.

Table 3. Species of animals infested and drugs of choice administered.

		Treatment of choice undertaken		
Species of animals	Frequency	Percent	Ivermectin	diazinon
bovine	81	77.9	50.6	49.4
canine	17	16.3	88.2	11.8
ovine	5	4.8	60.0	40.0
equine	1	1.0	100	0
Total	104	100.0		

DISCUSSION

External parasites cause a serious impact on animals as they feed on body tissues such as blood, skin and hair of animals. The annoying effect of different fly species on feeding animals should also be considered. The wounds and irritation produced by the bite of external parasites especially by ticks and mites often result in discomfort and secondary bacterial infections. Hence, these parasites cause great economic losses by lowering the immune system of animals, reduction of production and reproduction, causing wounds and also result in death (Singla, 1995).

As the eggs of ectoparasites including different fly species hatches abundantly during warm and moist periods of the year, the highest level of ectoparasite infestation was encountered during the season when maximum rainfall occurs. Spring and autumn periods with optimum rainfall are also potential ectoparasite infestation periods because the environmental conditions are favorable for the multiplication of flies and other ectoparasites. The lowest infestation was recorded during winter when lowest rainfall occurs.

Ectoparaciticides are antiparasitic formulations that are intended to kill ectoparasites like ticks, mange mites, lice, fleas and other insects that present or feed on the animal's body surface. The drugs' having such killing effects of ectoparasites includes organophosphates (e.g diazinon), carbamets (e.g aldicarb), organochlorines (e.g DDT), pyrethroids and an endectocide ivermectin (Tripathi, J.D., 2010). Diazinon and ivermectin have been found recorded as the only two drugs used extensively at the veterinary clinic of university of Gondar. This is in contrast to the recommendations of the study conducted in Brazil which underlines that frequent use of an acaricide combined with underdosage, overdosage or

inadequate spraying is the major cause of the development of resistant population (J. Furlong and S. Martins, 2000).
With respect to the macrolactons, ivermectin, doramectin and abamectin presented efficacies <95% in some cases. However, these compounds are not recommended for use on lactating cows, since they leave residues in the milk. However, these compounds can be used on other categories of herds to reduce the non-parasitic instars in pastures as part of an integrated management program, as observed by Castro (J. J. De Castro, 1997).
The research conducted by Landim et al (2006) also underlines the combined use of synthetic pyrethroides and organophosphates as they have a synergetic accaricide effect. The formulations containing this combination were more effective than formulations containing SP (synthetic pyrethroids) or OP alone. The authors reported that SP and OP used separately had maximum efficacy levels of 43.6% and 46.7%, respectively, while the SP + OP associations showed efficacy between 75.5 and 97.7%. This result was also observed by Furlong et al. (2007), who reported a small increase in efficacy of acaricides containing a combination of SP and OP on R. microplus populations.
Bovines are found the most infested species especially by ticks as they spend most of their day by roaming and grazing over a large area including forests where the population of ticks is high. Forests and large trees are potential sites of tick multiplication because of the moisture under such large trees is favorable and preferable by ticks. This is in line with what Regina vet said that animals that venture into densely wooded areas and tall grass can very easily pick up a tick of two or more (http://www.cbc.ca/news/canada/saskatchewan/regina-ticks-2016-veterinarian-1.3511128).

CONCLUSION AND RECOMENDATIONS

Ectoparasites are major causes of mortality and reduced productivity in domestic livestock. The insects cause this damage directly by feeding on or parasitising livestock, annoying, irritating, or indirectly, by transmitting livestock diseases. Common external parasites include horn flies, lice, ticks, mange mites, fleas and grubs. The level of infestation increases greatly during spring, summer and autumn seasons when there is favorable environmental conditions for their multiplication.
An ectoparasiticide is an antiparasitic drug used in the treatment of ectoparasitic infestations. These drugs are used to kill the parasites that live on the body surface. Permethrin, Diazinon, lindane, dicophane, benzyl benzoate, ivermectin and crotamiton are well known ectoparasiticides. The differences in efficacy of these acaricides can be related to the way they are used, such as inadequate spraying, underdosage or overdosage and/or high frequency of use causing the development of resistant populations.
Based on the above conclusions the following recommendations are forwarded

- To control infestation satisfactorily throughout the season, use self-treatment insecticides like ear tags or routinely apply spray, pour-on, spot-on or dust chemicals.
- Avoid intensive use of chemical formulations as it leads to loss of efficacy of the base molecules because of the development of resistant tick populations.
- During Applying take measures to minimize environmental contamination and toxicity to workers who apply them
- Minimize the use of ivermectin and rather use other topical acaricides because it has potential harmful residues in meat and milk

- Rather than using a single drug extensively for a long time it is better to use different drugs like organophosphates and carbamets in combination to get their synergetic effect

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