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Ivermectin Versus Selamectin and Fipronil as Ectoparasite Treatment in Cats and Dogs: A Literature Review

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ABSTRACT

Ectoparasite is commonly found on the skin and can cause dermatological problems. In veterinary practices, ivermectin, selamectin, and fipronil are commonly used to treat ectoparasitosis. This article aims to deeply examines the indications and contraindications of ivermectin, selamectin and fipronil. Ectoparasites are commonly found in cats and dogs and make up a large percentage of cases compared to other diseases. Therefore, it is important to have an understanding of the drugs that are effective against ectoparasites. In the past, ivermectin was a popular antiparasitic drug due to its high efficacy. However, its safety is not directly proportional its efficacy. Ivermectin has adverse effects, as evidenced by numerous case reports of overdose, intoxication, and interference with certain organ functions. In the field of pharmacology, many new drugs have been developed with the expectation of improved efficacy and safety. Two examples of such drugs are selamectin and fipronil. This article allows veterinarians and other readers to compare the safety and efficacy of these drugs before administering them to their patients.

Keyword: ectoparasite treatment, fipronil ivermectin, selamectin, small animals

INTRODUCTION

Parasites are organisms that live inside other organisms, called hosts, and exploit them. The largest animal phylum on Earth, the Arthropoda, is commonly used as a host by parasites (Carol, 2015). Parasites are divided into two types, namely ectoparasites and endoparasites, both of which can cause health problems (Nasution et al., 2018). These health problems cause skin manifestations and mainly affect pets such as dogs and cats (Fauziah et al., 2020). Ectoparasites cause direct physical damage to the skin, resulting in various skin manifestations. In addition, they can transmit microorganisms that lead to secondary infections (Carol, 2015). Common ectoparasites that affect pets include lice, fleas, ticks, and mites, which can causes diseases such as scabies, toxocariasis, and demodicosis (Shiveraw, 2018). Some of these diseases are parasitic zoonotic (Nasution, 2018). Timur et al. (2015) found that parasites were responsible for the majority of skin diseases in Kintamani dogs from 2009 to

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2013, accounting for 15.2% of cases. In addition, a survey of small animals in England found that 797 (21.4%) of the 3,707 consultations were related to dermatological problems, with 80% of these problems attributed to parasites (Hill et al., 2006). In Iran, 64% of dogs are commonly infested with parasites, and in Egypt, this is particularly prevalent in stray and shelter dogs (Zineldar et al., 2023). Therefore, appropriate antiparasitic drugs are necessary to address the problem.

Ivermectin has been widely used as a broad-spectrum antiparasitic drug since 1981 (Panayotova & Pencheva, 2005). However, its efficacy has been surpassed by newer drugs that are easier to use. In addition, ivermectin can lead to increased levels of intoxication and organ dysfunction. Selamectin and fipronil are two antiparasitic drugs commonly recommended by veterinarians. This article provides a brief review comparing the efficacy, indications, and contraindications of ivermectin, selamectin and fipronil to help veterinarians make informed decisions when selecting the appropriate therapeutic options to treat ectoparasitosis.

Selamectin is administered topically and has been shown to be highly effective against *S. scabiei* infestations in dogs, with efficacy rates of more than 95%, 30%, and 100% on day 60. In addition, selamectin has been shown to completely eliminate *O.cynotis* mites in 100% of dogs on day 60 (Oh et al., 2004).

Fipronil is highly effective in eliminating mosquitoes, specifically *A. albopictus* (≥ 93.4% by day 21 and 86.9% by day 28), *A. aegypti* (≥ 91.0% by day 35), and *C. pipiens* (≥ 90.4% by day 28). For *A. albopictus*, the efficacy rates of fipronil were more than 97.1% from 24 hours to day 28; more than 98.0% for the first three weeks, and 75.7% on day 35. For *C. pipiens*, the efficacy rates of fipronil were 93.8% on day 7 and 30.9% on day 28 (Fankhauser et al., 2015). In eradicating fleas, the efficacy rates of fipronil were 97.6% and 98.6% on day 14 and 30, respectively (Yonetake et al., 2019).

REVIEW

This study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method.

Information sources

The results of the literature review were summarized and grouped based on the indications and contraindications of each drug. The data were collected from Google Scholar, Research Gate, and PubMed from 1999 to 2021 using the keywords ivermectin, ivermectin indications, ivermectin efficacy, ivermectin side effects, selamectin indications, selamectin side effects, fipronil indications, fipronil side effects, ectoparasite therapy in dogs and cats, and the combination of these keywords. Initially, 57 articles were read 57 articles were marked for future review (Figure 1).

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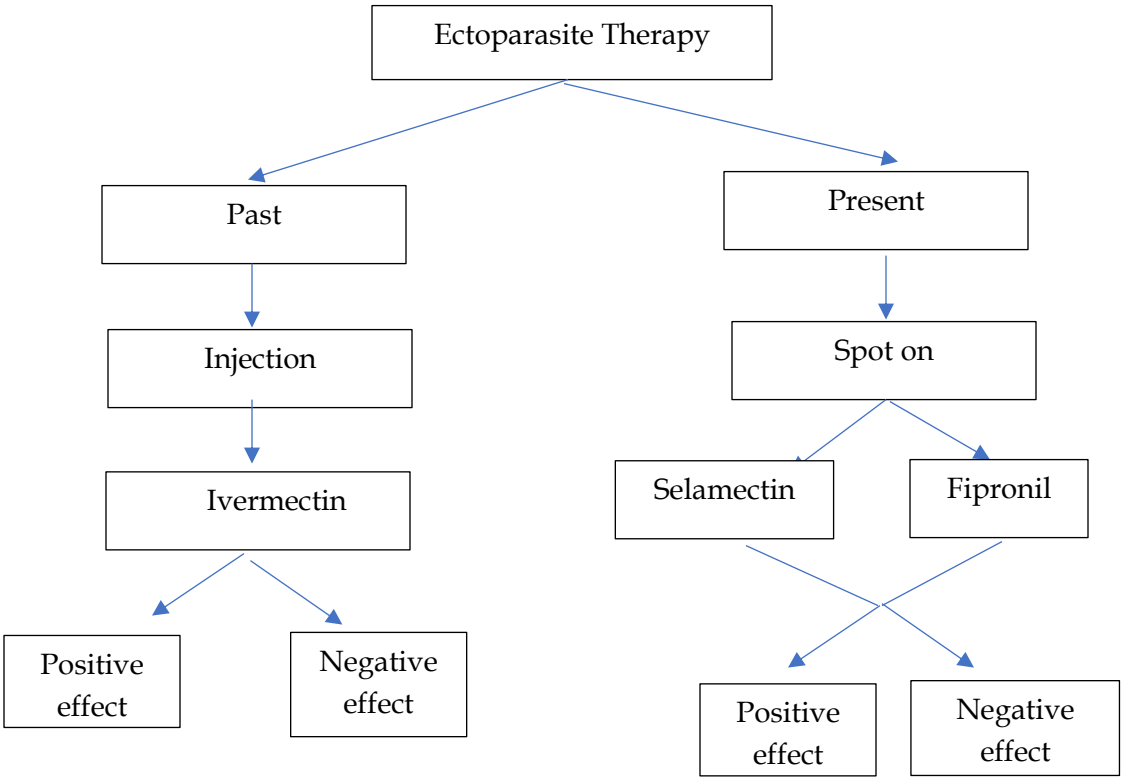

Figure 1. Chart flow ectoparasite review

Inclucion Criteria

The inclusion criteria were articles written in English on treatment for ectoparasite infection in small animals using ivermectin, selamectin, and fiproni.

DISCUSSION

Ivermectin Mechanism

Ivermectin has broad-spectrum molecules. It is commonly used to control ectoparasites and endoparasites (Bilwal et al., 2020). Ivermectin is a derivative of avermectin and belongs to the macrocyclic lactone group produced by *Streptomyces avermitilis* (Yanuartono et al., 2020). It has been found to be effective against nematodes and other endoparasites with an efficacy rate between 94% and 100% (Dong et al., 2020). Ivermectin was first discovered in 1975 and widely marketed by Merck Sharp and Dohme in 1981.

Ivermectin can cause neurotoxicity by affecting the level of glutamic chloride ions in the parasite, causing chloride channels to open and preventing the release of the gamma-aminobutyric acid (GABA) neurotransmitter (Purnamaningsih & Ida, 2002). This results in paralysis due to the hyperpolarization of nerve cells, ultimately leading to the death of the parasite (Bilwal et al., 2020). Furthermore, it inhibits the transmission of proteins between inhibitory motor neurons and muscles. However, it has minimal effect on the transmission of

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neuromuscular stimuli (Dong et al., 2020). Since mammals have only one large central GABAergic synapse, the blood-brain barrier is relatively resistant to ivermectin. However, high doses of the drug can result in increased penetration of the blood-brain barrier, leading to toxicity. Many species of mammals exhibit central nervous system (CNS) depression and ataxia as a result of increased GABAergic synaptic inhibition (Tripathi & Soodan, 2012).

Ivermectin for Pets

The efficacy of ivermectin depends on the correct dosage, whether administered by injection or orally (Purnamaningsih & Ida, 2002). In addition, an otic suspension containing 0.01% of ivermectin is used to control cyanotic otodectic disease (Bowman et al., 2001). It is important to note that the pharmacokinetics of a drug are associated with its pharmacological efficacy. Ivermectin is slowly absorption, low metabolism, wide distribution, and slow excretion in the body. Its efficacy may be affected by various factors, including drug application, formulation, animal species, age, and physical and physiological conditions (Canga et al., 2009). The following are some of the reports on the different uses of ivermectin.

Ivermectin Intoxication

Although ivermectin is considered effective in eradicating endoparasites and ectoparasites due to its broad-spectrum activity, inappropriate use can result in ivermectin poisoning (Yanuartono et al., 2020). Most cases of poisoning are due to overdoses of the compound. However, certain breeds have been described as having an increased susceptibility to ivermectin toxicosis, and severe anaphylactic reactions can occur due to the sudden and massive release of toxins from the parasite (Canga et al., 2010). In addition, the use of ivermectin, even at recommended doses, can have negative effects on organ function. Many reported cases have been associated with ivermectin toxicity. The following are some of the reported cases of contraindications to the use of ivermectin.

From these cases, it can be concluded that there is no specific antidote for ivermectin poisoning. The only available therapies are management, supportive care, and symptomatic treatment (Bilwal et al., 2020). Several studies with a certain number of samples also reported the adverse effects of the use of ivermectin as shown in Table 1.

Table 1. Intoxication of Ivermectin

Host	Application	Dose	Parasite	Results	Reference	Research Location
16 dogs	Subcutaneous injection of ivermectin 1%	400µg/kg	Tick infestation	The efficacy rates were 60% and 72%, lower than the use of other drugs due to the	Purnamaningsihg & Ida (2002)	Yogyakarta

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				length of time it takes for the number of ticks to decrease after administration by subcutaneous injection		
Three-year-old female Persian cat weighing three kilograms	Ivermectin injection	0.3mg/kg administered twice with 14 days interval	Scabies (*Notoedres cati)*	Hematology results = increased levels of white blood cells Treatment results = reduced lesion and healed by day 8 after treatment	Amir et al. (2020)	Bali
Five domestic cats (three females and two males) aged between six months and one year	Subcutaneous injection of ivermectin	200 µg/kg	Scabies (*Notoedres cati)*	A negative scraping result after two weeks of treatment	Kumar et al. (2008)	Dermatology Unit of Madras Veterinary College Teaching Hospital, India
Fifty-eight dogs aged more than seven weeks and weighing more than four kilograms	Ivermectin perorally	500 µg/kg	Demodicosis	Good efficacy	Paterson et al. (2014)	Not disclosed

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Fourty-five cats	Topical ivermectin smeared on the back in between the scapula	0.1 ml/kg administered between twice and four times with 14 days interval	Otoacariasis, cheyletiellosis, and toxocariasis	The efficacy rates were 96% and 100% for otoacariasis and toxocariasis, but one *Cheyletiella* egg was found after four times of ivermectin administration	Page et al. (2000)	Canada
Kittens aged four weeks and above	Ivermectin otic suspension containing ivermectin 0.01% (Acarexx™; Blue Ridge Pharmaceutics Greensboro, NC)	0.5ml/ear applied directly into the ear hole	Adult mites	Good efficacy in getting rid of adult mites	Bowman et al. (2001)	Not disclosed

Selamectin Mechanism

Selamectin belong to the avermectin class of drugs, which are effective against heartworms and ear mites in dogs and cats. It can also eliminate mites and ticks in dogs and treat ascariasis. The molecular formula of selamectin is $C_43H_63NO_{11}$. Selamectin works by enhancing the effects of glutamate, which inhibits electrical impulses and nerve muscles in invertebrates. This causes hyperpolarization and paralysis of the nervous system. If administered at the recommended dose, this drug is not toxic to animals. In addition, selamectin works by opening chloride channels, which prevents the effects of GABA and the transmission of nerve signals. This results in the blockage of neuromuscular transmission and disturbance of neuronal polarity, leading to paralysis and death of ectoparasites. However, it is important to note that each species has a unique mechanism that depends on the concentration of the drug administered. Oral administration of the drug can cause vomiting, rolling, shaking, anorexia, and loss of balance (El-Saber Batiha et al., 2020).

Fipronil Mechanism

Fipronil is belong to the phenylpyrazole class of drugs, which bind to skin fat to eliminate ectoparasites upon contact. It is

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commonly used to kill fleas, brown dog ticks, American dog ticks, *Amblyomma* sp., and *Borellia* bacteria in dogs and cats. Fipronil works by disrupting the flow of chloride ions through chloride channels regulated by GABA, which interferes with CNS activity. Biochemical tests have shown that fipronil binds with higher affinity to insect GABA receptors than to vertebrate GABA receptors. This difference in affinity may explain the selective toxicity of fipronil (Gant et al., 1998). If an overdose causes lethal damage to the animal, the label must indicate the age. In addition, it should not be used for pregnant animals, kittens less than 12 weeks old, or puppies less than 10 weeks old (Ramesh, 2018).

Development of Selamectin and Fipronil

Since 2000, veterinary researchers have tested selamectin on dogs and cats with ectoparasite infestations, including ticks, mites, and fleas. By understanding the characteristics of a drug, its efficacy can be determined. Efficacy represents a decrease in the incidence of a disease in a treated group. This is compared to an untreated group under optimal conditions to determine the efficacy of the drug.

Research conducted from 2000 to 2021 suggested that selamectin has shown high efficacy in eliminating lice with an efficacy rate between 94% and 100% (Six et al., 2000) and mites with an efficacy rate between 93% with one dose and 100% with two doses (Shanks et al., 2000). In addition, selamectin has shown high efficacy in eliminating lice with efficacy rates of 92.1%, 99.0%, and 99.8% on days 30, 60, and 90, respectively (Boy *et a*l., 2000). Selamectin has also shown high efficacy in eliminating fleas with efficacy rates of 81.5%, 94.7%, and 90.8% for dogs and 79.8%, 98%, and 96.2% for cats on days 7, 14, and 21, respectively (McTier et al., 2000). Moreover, other research suggested that selamectin eliminated fleas and ticks with high efficacy rates. Schenker et al. (2023) found that 74.4% of fleas were eliminated, while Dryden et al. (2013) found that 60.4% and 91.4% of fleas were eliminated in 24 hours and 48 hours, respectively. Geurden et al. (2017) also found that more than 95.8% of ticks were eliminated in four weeks. On the other hand, Becskei et al. (2017) found that 100% of fleas were eliminated in five weeks, while Yonetake et al. (2019) found that 99.5% and 99.9% of fleas were eliminated on days 14 and 30, respectively.

Furthermore, fipronil is highly effective in eliminating mosquitoes, specifically *A. albopictus* (≥ 93.4% by day 21 and 86.9% by day 28), *A. aegypti* (≥ 91.0% by day 35), and *C. pipiens* (≥ 90.4% by day 28). For *A. albopictus*, the efficacy rates of fipronil were more than 97.1% from 24 hours to day 28; more than 98.0% for the first three weeks, and 75.7% on day 35. For *C. pipiens*, the efficacy rates of fipronil were 93.8% and 30.9% on days and 28, respectively (Fankhauser *et al*., 2015). In eliminating fleas, the efficacy rates of fipronil were 97.6% and 98.6% on days 14 and 30, respectively (Yonetake et al., 2019).

Advantages of Using Selamectin and Fipronil

Bartonella henselae causes cat scratch disease in humans, which is a recognized zoonotic disease. The main vector is *Ctenocephalides felis*, and the main mode of

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transmission of *B. henselae* infection between cats and humans is through infected flea feces. Selamectin is used to prevent transmission of *B. henselae* by *Ctenocephalides felis*. No cats showed clinical signs of bartonellosis in the studies. In addition, none of the cats treated with selamectin tested positive, demonstrating the efficacy of selamectin in preventing the transmission of *B. henselae* by fleas to cats (Franc et al., 2015).

Geuden et al. (2017) found that selamectin was not less effective than fipronil and was more effective on days 30 and 60. In fact, selamectin is a more potent insect growth regulator than fipronil (Panwar & Kumar, 2011). Topical administration of selamectin spot-on formulations at minimum doses within 12 hours and six hours after infestations for 28 days consistently and rapidly eliminated lice within five weeks (Sillabecskei, 2017). According to Wakakotonetake et al. (2019), selamectin significantly reduced the numbers of *H. longicornis* on patients at veterinary clinics in Japan by 96.4% within 48 hours and more than 91.7% within 48 hours after weekly re-infection for 35 days.

Topical selamectin is more effective than oral spinosad in preventing weekly tick infestations and against *Ctenocephalides felis* from day two to 30 (Dryden et al., 2013). However, fipronil was found to be resistant to *R. sanguenus* (Eiden et al. 2015). Fipronil is 100% effective in killing fleas in dogs and cats and has no known side effects (Tuzer et al., 2010). To treat naturally occurring *Sarcoptes scabiei* and *Otodectes cynotis* infestations in dogs, selamectin is administered topically. The efficacy rates of of selamectin against *S. scabiei* infestations in dogs are more than 95%, 30%, and 100% on day 60. Meanwhile, against *O. cynotis*, selamectin has been shown to eliminate mites in 100% of dogs on day 60 (Oh et al., 2004).

Fipronil is more effective than ivermectin for mild mite infestations, especially if it is administered twice at a four-week interval (Purnamaningsih & Ida, 2002). Fipronil, fipronil sulfone, and fipronil sulfide are collectively known as fiproles. As part of their chemical monitoring program, environmental agencies collected water samples and analyzed them using the liquid chromatography-mass spectrometry (LC-MS) or quadrupole-time-of-flight mass spectrometry (Q-TOF-MS) methods. The results indicated a high environmental risk of fipronil and a moderate risk of imidacloprid to aquatic ecosystems. The highest concentrations of fipronil and imidacloprid were found downstream of the wastewater treatment plant, which supported the hypothesis that many pesticides from animal flea products could enter the aquatic environment through the domestic water supply. These findings highlight the necessity of re-evaluating the environmental risks associated with the use of parasitic products for pets and the corresponding risk assessment procedures prior to regulatory approval (Perkins et al., 2021) (Figure 2).

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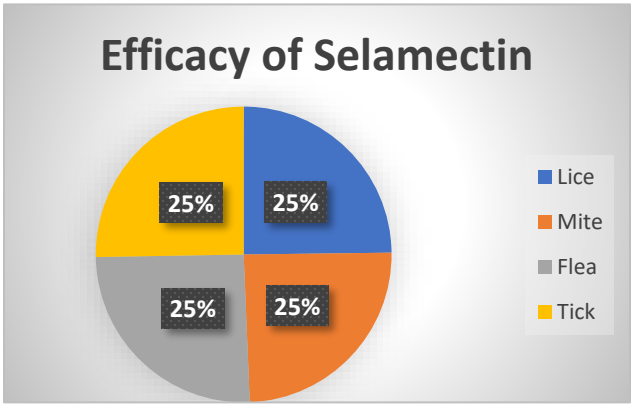

Figure 1 Diagram of The Efficacy of Selamectin

Research on selamectin conducted from 2000 to 2021 shows high efficacy rates between 94% and 100% in eliminating lice (Six et al., 2000). In addition, more than 93% of mites were eliminated with one dose and 100% with two doses (Shanks et al., 2000). Meanwhile, 92.1%, 99.0%, and 99.8% of lice were eliminated on days 30, 60, and 90, respectively (Boy et al., 2000). In comparison, 81.5%, 94.7%, and 90.8% of fleas in dogs, and 79.8%, 98%, and 96.2% of fleas in cats were eliminated in days 7, 14, and 21, respectively (McTier et al., 2000). Finally, selamectin was shown to eliminate fleas with an efficacy rate of 74.4% (Schenker et al., 2003).

Table 2. Administration of Selamectin

Combination	Animals	Dose	Administration	
Selamectin	Dogs and cats aged at least six weeks	6-12 mg/kg	Spot on (every two weeks within one month)	Not for weak pets, no action for lungworm and demodex (Hany, 2017)
Selamectin	Rabbits	6-20 mg/kg	Spot on (every one week)	Effective for *P. cuniculi* (McTier et al., *2003)* Effective for fleas, ticks, and mites (Peter, 2016)
Selamectin	*Paguma larvata*	15 mg/kg	Spot on (every two weeks repeated three times)	Effective for *Notoedres spp* (Olivieri et al., *2015)*
Selamectin	Other small mammals	10-12.4 mg/kg	Spot on	Effective for *Myobia musculi, Mycoptes musculinus, Radfordia ensifera, Radfordia affinis and* blood

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				sucking lice *(Polyplax serrata* and *Polyplax spinulosa*) (Peter, 2016)
Selamectin	Birds	Undefined	Spot on	Effective for *Dermanyssus gallinae* (Peter, 2016)
Selamectin and sarolaner	Cats	6 mg/kg and 1 mg/kg	Spot on	Effective for *H. longicornis* (Yonetake et al., 2019)

Table 3. Administration of Fipronil

Combination	Animals	Dose	Administration	
Fipronil	Cats and dogs aged a minimum of two days and weighing a maximum of 6.6 kg	6.7 mg/kg	Spot on	It is not for rabbits because it can be fatal (Hany, 2017).
Fipronil-permethrin	Cats and dogs aged a minimum of 12 weeks	6.7 mg/kg (F) 60 mg/kg (p)	Spot on	
Fipronil/s-methoprene	Cats weighing a minimum of 1 kg, dogs weighing a minimum of two kilograms, ferret aged a minimum of six months	6.7mg/kg (F) 6.0mg/kg (S-m)	Spot on	It is not for rabbits because it can be fatal (Hany, 2017).
Fipronil/s-methoprene/amitraz	Dog weighing a minimum of two kilograms	6.7mg/kg (F) 6.0mg/kg (S-m)	Spot on	Amitraz can eliminate ticks rapidly. It is not for rabbit because it can be fatal (Hany, 2017).

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		8 mg/kg (a)		
Fipronil 0.25% solution	Green iguana infected with *Hirstiella sp.* (Farmaki et al., 2013)		Spot on	
Fipronil 10% w/v	Cats weighing 1 kg (Rohdich et al., 2018)	7.5-15 mg/kg (0.5 ml)	Spot on (every four weeks)	
	Dogs weighing 2-10 kg	0.67 ml	Spot on	
	Dogs weighing 10.1-20 kg (Bonneau et al., 2010)	1,34 ml		
Fipronil 0.005%	Gerbils (Rodentia)	~120 g	Oral	100% of *Xenopsylla spp.* were eliminated (Poché *et al.*, 2018)

Side Effects of Selamectin and Fipronil for Pet Animals

Geuden et al. (2017) reported that selamectin has no known side effects, is safe to be administered monthly, and is effective against natural fleas in cats. However, it does not reduce the clinical signs of pruritus, erythema, scales, and undulating papules, or *Sarcoptes scabiei* infestations on the skin. Positive control products achieved similar results. Tuzer et al. (2010) reported that selamectin is safe and effective against *Sarcoptic scabies* and ear mites in dogs. In addition, Lecru (2019) suggested that there are no adverse effects on dogs that have been treated with selamectin. In comparison, the combination of permethrin and fipronil can be well-tolerated and is effective in rapidly controlling *Neotrombicula* mites in dogs.

Selamectin and Fipronil for Veterinary Use

Since its introduction in 1999, selamectin has been widely used by veterinarians in many countries, particularly in America, Europe, and Asia. Selamectin, along with fipronil, is commonly used in countries with high populations of dogs, cats, and other pets, such as iguanas and geckos. Selamectin

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is a broad-spectrum drug that is effective against ectoparasites and endoparasites and has a long-lasting effect. It is also safe to use on exotic animals (Peter, 2016).

According to Adverse Drug Experience (ADE) data from the Australian Pesticides and Veterinary Medicines Authority (APVMA), the use of fipronil between 1996 and 2003 resulted in several contraindications or side effects in cats treated with fipronil. These side effects included alopecia, coat discoloration, pruritus, erythema, neurological symptoms, and gastrointestinal symptoms. For dogs, the side effects included skin reactions, neurological symptoms, and gastrointestinal symptoms. Fipronil can be fatal for rabbits. It was found that 32 rabbits died after fipronil spray treatment, while 13 others recovered. The total incidence of the fipronil-related incidents in Australia was 2.7 times higher than any other ADE recorded globally. Therefore, it is recommended to strictly follow the instructions on the packaging label. It is also important to note that since 1993, all fipronil products, whether spray or spot-on, have been labeled as unsuitable for use in rabbits.

CONCLUSION

Regardless of the content, the use of anti-ectoparasite drugs through spot-on application is safer and more practical than other methods. This is because the general public can only purchase spot-on products according to the weight of the animal, minimizing the risk of overdose. Ivermectin has been avoided due to its harmful side effects, such as intoxication, and potential organ damage. Selamectin has been used by veterinarians worldwide since 2000 due to its high level of safety and efficacy rates between 94% and 100% in eliminating ectoparasites. However, fipronil still holds the record despite its contraindications and side effects, especially in rabbits, which can be fatal. Therefore, the use of fipronil must be strictly in accordance with the recommendations on the drug packaging label.

Selamectin will continue to be used for treatment due to its high level of safety and efficacy in eliminating ectoparasites. However, further studies are needed to evaluate the efficacy of other anti-ectoparasitic drugs and promote advancements in veterinary medicine. This article suggested that the effectiveness of selamectin or fipronil spot-on treatments is influenced by several factors, including regular administered of the drug, correct dosage, and cleanliness of the animal, which must be supported by the pet owner.

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