CPD article

An updated review of the indications and adverse drug events associated with the ectoparasiticides used in small animal practice

The global burden of ectoparasitic infestations is exacerbated by the lack of licensed vaccines, meaning safe and effective ectoparasiticide drugs are vital to their prevention and treatment. However, adverse clinical consequences of treatments for ectoparasites affect thousands of cats and dogs in the UK each year. The unpredictable outcomes of these treatments in some animals can be associated with undesirable consequences and there is a lack of knowledge surrounding their use. This article discusses indications of the major classes of ectoparasiticides used in small animal practice and highlights the types of adverse drug reactions associated with the parasiticides used to treat ectoparasite infestations in dogs and cats. Overall, the incidence of adverse drug events reported in relation to ectoparasiticide use, compared to the total doses administered globally, is small. The potential consequences for animal and human health of not using ectoparasiticides is likely to be more serious than the current rate of adverse drug reactions being reported. The benefits of protection from ectoparasite infestations will therefore outweigh the potential consequences of adverse events associated with such treatment.

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Ectoparasites that infest cats and dogs represent a significant threat to animals' health and welfare. In a recent UK survey, tick attachment prevalence in dogs ranged between 28–32%, indicating a widespread problem (Abdullah et al, 2016). It is important to treat, prevent and control ectoparasite infestations for the health of the animal, as well as for public health, because of the zoonotic potential of some ectoparasites (Mencke, 2013). Ectoparasites can cause various dermatological signs, such as pruritus, allergy and even anaemia in heavy infestations (Beugnet et al, 2014). Furthermore, they can act as vectors for various pathogens causing disease, hence ectoparasiticide treatments are important in restricting the spread of these pathogens (Geurden et al, 2017a).

Diagnosing an ectoparasite infestation involves skin scrapes, hair plucks, hair combing, acetate strips and visual examination (Wall and Shearer, 2008). Fleas can be found by thoroughly combing the host with a fine-toothed flea comb (Beugnet et al, 2016). Palpation and visual examination by systematically pushing the hair against the hair growth will reveal any ticks living on a host (Navarro et al, 2016). Definitive diagnosis of mite infestations requires clinical suspicion based on dermatological signs and microscopic identification of the mite (Romero et al, 2016). A variety of surface mites and deep mites can infest companion animals. Superficial skin scrapings are sufficient to find *Sarcoptes scabiei*, but deep skin scrapings are necessary to detect *Demodex* mites (Paterson et al, 2014). Lice and their eggs are easily visible to the naked eye so visual examination of the host is adequate to diagnose a lice infestation (Gunnarsson et al, 2005).

In order to successfully control ectoparasite infestations, it is necessary to kill adult parasites, break the lifecycle and control

environmental contamination (Beugnet et al, 2016). Management of ectoparasite infestations can be through chemical means, such as use of ectoparasiticides and non-chemical means such as vacuuming the home environment, particularly during flea infestations (Rust and Dryden, 1997). While environmental treatment is of clear value during flea infestations, egg laying will only be prevented and the flea lifecycle broken by using an effective adulticide or insect growth regulator on the animal. Ectoparasiticides are among the most commonly used drugs in companion animals. They come in the form of collars, spot-ons, sprays, injections, and tablets (Maddison et al, 2008). Generally speaking, the expected benefits of treatment should be far greater than the risk of related harmful reactions (Dyer et al, 2010). However, some ectoparasiticide drugs can cause morbidity and mortality as a result of adverse drug reactions. Therefore, it is important to report any adverse events associated with a product used in field conditions (National Office Animal Health [NOAH], 2017h).

This article reviews the mechanisms of therapeutic actions and adverse health complications associated with the common ectoparasiticides used in small animal practice. Some of the common problems associated with the use of ectoparasiticides in companion pets are discussed. Recommendations to pet owners and veterinary professionals are also provided.

Major ectoparasitic infestations of cats and dogs

In the following sections, the major groups of ectoparasites that have a significant impact on the health and welfare of cats and dogs in the UK are described.

Fleas

Ctenocephalides felis, or the 'cat flea', is the main species of flea infesting cats and dogs in the UK and many other countries (Taenzler et al, 2014). They are more common in multi-pet households (Bond et al, 2007). Adult fleas feed on the blood of the host, so heavy infestations can cause anaemia (Qureshi et al, 2015). The adult cat flea can cause irritation and pruritus, compromising the animal's welfare (Varloud and Hodgkins, 2015). If severe, the pruritus can lead to hair loss and skin lesions (Bouhsira et al, 2012). Flea allergy dermatitis is a result of a hypersensitivity reaction to the salivary proteins introduced to the host by the flea during feeding (McCoy et al, 2008). It is characterised by pruritic dermatitis and skin inflammation, with lesions localised to the caudomedial thigh, lumbosacral area and the base of the tail (Bruet et al, 2012). Erythema, alopecia, excoriation and papules or pustules can be observed on inspection of a dog with flea allergy dermatitis (Bonneau et al, 2009). Fleas can also act as vectors of pathogens such as *Rickettsia* spp. and *Bartonella* spp., and they are the intermediate host of the tapeworm *Dipylidium caninum* (Conboy, 2009; Bitam et al, 2010).

Ticks

Ixodes ricinus, followed by *Ixodes hexagonus*, are the most prevalent tick species found on dogs in the UK (Jameson and Medlock, 2011). Other tick species found on dogs include other *Ixodes* species, *Dermacentor reticulatus* and *Rhipicephalus sanguineus* (Abdullah et al, 2016). An increase in temperature and a decrease in the length of winter as a result of global warming has led to more *Ixodes* species populations developing in Europe (Beugnet and Marié, 2009). Tick infestations are reported less frequently in cats than dogs (Geurden et al, 2017a). In addition to causing irritation ticks feed on the blood of their host, so they can cause blood loss anaemia (Varloud and Hodgkins, 2015). Ticks can transmit a number of pathogens while feeding on their host (Wengenmayer et al, 2014). Tick-borne diseases include those caused by pathogens, such as *Babesia* species, *Rickettsia* species, *Ehrlichia* species and *Borrelia* species (Shaw et al, 2001). Ticks can also act as vector for viruses, such as viral tick-borne encephalitis and louping ill virus (Chomel, 2011). In many instances, a feeding period of at least 24 hours is necessary after the attachment of the tick before the transmission of the disease-causing pathogen can occur (Taenzler et al, 2015).

Mites

Common mite genera causing welfare concerns in companion animals include *Demodex*, *Sarcoptes*, *Otodectes*, *Notoedres* and *Cheyletiella.* Large mite infestations can be highly pruritic and contagious (Ghubash, 2006). *Demodex* mites are considered to be commensal organisms of dogs and when numbers increase they can cause inflammatory disease (Six et al, 2016). Dogs suffering with sarcoptic mange present with erythema, yellow crusts and severe pruritus, all of which can be accompanied by secondary bacterial pyoderma (Becskei et al, 2016a). Puppies and kittens appear to be most susceptible to *Otodectes cynotis* infestation, as immunity is usually acquired with age (Curtis, 2004). Notoedric mange is a highly contagious disease, predominantly of cats and kittens, which is capable of causing extreme pruritus and crusting lesions (Fisher and Shanks, 2008). *Cheyletiella* species are non-burrowing mites which can infest cats and dogs asymptomatically or cause variable pruritus (Wagner and Stallmeister, 2000).

Lice

Lice infestations are rare on dogs, but if present they are associated with disease or neglect, usually presenting in either very young or very old animals (Stanneck et al, 2012b). Chewing lice feed on dermal debris and exudate from skin lesions, whereas sucking lice feed on blood (Arther, 2009). Heavy infestations can result in intense irritation, pruritus and self-trauma. Scratching can lead to alopecia, crusts and secondary bacterial involvement (Pollmeier et al, 2002). Like fleas, the chewing louse, *Trichodectes canis*, is an intermediate host of *Dipylidium caninum* (Kužner et al, 2013).

Current management strategies

There are a variety of ectoparasiticides available from different chemical classes, and non-chemical support measures that can be used to prevent ectoparasite infestations. A survey of Canadian animal shelters showed that 41–50% of the participating shelters administered all animals with an ectoparasiticide. Cost was identified as a critical factor in deciding whether to use antiparasitic treatments in the shelters and which treatments to use (Schurer et al, 2015). Besides causing significant morbidity

and mortality among companion animals, ectoparasites have a large economic impact (Rafiqi et al, 2016). Over 40% of the global companion animal market is represented by parasite control, with half of this being ectoparasite control (Witchey-Lakshmanan, 1999). In 2009, the market for antiparasitic drugs in carnivores was worth approximately $3.5 billion (USD), or 45% of the market for companion animal health care (Beugnet and Franc, 2012).

Chemical approach

Ectoparasiticides can be split into two groups – insecticides or acaricides and insect growth regulators (Table 1). Insecticides or acaricides predominantly act on arthropod nerve axons. Ectoparasiticides can be neuroinhibitory (such as fluralaner and fipronil) or neuroexcitatory (such as deltamethrin and imidacloprid), causing flaccid or spastic paralysis (Beugnet and Franc, 2012). These drugs will be discussed in detail later. Voltage-gated sodium channels are a common target for ectoparasiticides, because of their action in the initiation and propagation of action potentials in many cells (Silver et al, 2010). IGRs mode of action is controlling the flea egg and immature stages (Rust and Dryden, 1997). The majority of the available ectoparasiticides are spot-on solutions (Beugnet and Franc, 2012). Once applied, the active ingredient can be found in sebum and sebaceous glands across the body (Cochet et al, 1997). Aside from treatments applied directly to the animal, insecticides and acaricides can be used in the home environment to help control ectoparasite infestations. Successful target areas for applying products include around cages, bedding and crevices between the floors, walls and ceiling (Blagburn and Dryden, 2009).

Fluralaner (Bravecto)

Bravecto (MSD Animal Health) contains fluralaner of the isoxazoline chemical class. It is an inhibitor of γ-aminobutyric acid (GABA)-gated chloride channels and glutamate-gated chloride channels. Fluralaner has high selectivity and potency for arthropod channels, compared to those in mammals (Gassel et al, 2014). Therefore, it is safe for use in companion animals, even at high doses. Neuronal signal transmission within the arthropod is blocked, leading to paralysis and death of fleas and ticks (Wengenmayer et al, 2014).

Fluralaner is available as chewable tablets for dogs. Bioavailability of oral fluralaner in dogs can be significantly increased by administering it with food (Walther et al, 2014b). Bravecto tablets are also effective at eliminating generalised demodicosis (Fourie et al, 2015) and scabies infestation, significantly reducing lesion severity and pruritus (Romero et al, 2016).

Fluralaner effectively kills adult fleas within 8 hours of flea infestation (Taenzler et al, 2014). This disrupts the flea lifecycle thus completely controlling egg laying, larval development and flea reproduction (Williams et al, 2014). Bravecto was found to

Table 1. Ectoparasiticides discussed in this article

Chemical class/ drug name	Mode of action	Product name	Presentation	Frequency of use	Species	Spectrum of activity
Isoxazoline - Fluralaner	Blocks GABA and glutamate-gated Cl channels	Bravecto	Tablet Spot-on	12 weeks 12 weeks	Dogs Dogs and cats	Fleas, ticks and mites (*Demodex* and *Sarcoptes* in dogs; *Otodectes* in cats)
Phenylprazole - Fipronil	Blocks GABA- and glutamate-gated Cl channels	Frontline	Spot-on	4 weeks	Dogs and cats	Fleas, ticks and chewing lice
Neonicotinoid - Imidacloprid	Blocks nicotinic acetylcholine receptors	Advantage	Spot-on	4 weeks	Dogs and cats	Fleas and chewing lice
Insect Growth Regulator - Lufenuron	Inhibits chitin synthesis	Program	Injection	6 months	Feline	Flea eggs and larvae only
			Oral suspension	4 weeks	Feline	
			Tablet	4 weeks	Dogs and cats	
Macrocyclic lactone - Selamectin	Opens chloride channels in peripheral NS	Stronghold	Spot-on	4 weeks	Dogs and cats	Fleas, chewing lice, mites *Otodectes*, *Sarcoptes*, roundworms
Oxadiazine - Indoxacarb	Blocks voltage-gated Na channels	Activyl	Spot-on	4 weeks	Dogs and cats	Fleas
Pyrethroid - Deltamethrin	Repellent and opens Na channels	Scalibor	Collar	5–6 months	Dogs	Fleas, ticks and flies

Based on Elsheikha (2017)

have almost 100% efficacy of tick killing within 12 hours of tick infestation (Wengenmayer et al, 2014). This aids the prevention of transmission of tick-borne diseases. A field study in which 383 dogs were given a single oral dose of Bravecto concluded that it was effective in controlling flea and tick infestations for 12 weeks (Rohdich et al, 2014). It was noted in this study that the 12-week efficacy of Bravecto could increase compliance because of the infrequent need for administration, compared to other ectoparasiticides.

Fluralaner is rapidly absorbed, well distributed to tissues and has a low clearance (Kilp et al, 2014). This could explain why the drug was detected in plasma for up to 112 days after a single oral administration. Supporting this finding, Bravecto tablets for dogs were reported to be 100% effective against repeated flea infestations for 4 months (Dryden et al, 2015). Six dogs were infested with 200 unfed adult *C. felis felis* and then treated with Bravecto. The dogs were infested eight more times during a 122-day evaluation period. A 100% reduction in flea count and 99.9% reduction in egg production was found upon inspection 48 hours after treatment of each infestation. This suggests that Bravecto is an effective insecticide for longer than the 12 weeks that the majority of studies have indicated. However, the study was on a very small number of dogs, so the reliability of the results needs to be confirmed in a bigger trial.

Bravecto is also available as a tri-monthly spot-on treatment for both cats and dogs. Fluralaner spot-on is rapidly absorbed transdermally into the skin, subjacent tissues and blood, and is distributed systemically (Kilp et al, 2016). The product has proven to be over 99% effective at treating *C. felis* and *I. ricinus* infestations in dogs for 12 weeks, even with shampooing and repeated water-immersion (Taenzler et al, 2016). Field and laboratory studies have found the product to be slightly less effective in cats. Bravecto spot-on for cats has proven at least 90% effective at reducing flea burden and at least 67% effective at controlling *I. ricinus* infestations for 12 weeks (Meadows et al, 2017; Geurden et al, 2017b). This lower efficacy in cats compared to dogs could be because of the more rapid elimination of fluralaner after topical administration in cats (Kilp et al, 2016).

Safety of Bravecto

Fluralaner chewable tablets are safe and well tolerated by dogs, even multi-drug resistance gene (MDR1) ($^{-/-}$) collies (Walther et al, 2014d). No treatment-related adverse reactions were found in many of the studies (Wengenmayer et al, 2014; Kilp et al, 2014; Dryden et al, 2015). Bravecto tablets have been found safe to give at five times the recommended therapeutic dose (Walther et al, 2014a). In clinical trials for Bravecto chewable tablets for dogs, several mild adverse reactions were observed (NOAH, 2017c). In pharmacovigilance reports, convulsions and lethargy have very rarely been described. The NOAH compendium details how fluralaner could compete with other drugs highly bound to plasma proteins, such as non-steroidal anti-inflammatory drugs (NSAIDs) or warfarin, but no such findings have been clinically proven. No drug interactions with commonly used veterinary products were apparent in these trials. Supporting this, Bravecto has been found safe to use with deltamethrin, milbemycin oxime and praziquantel (Walther et al, 2014c; Walther et al, 2014b).

In a 12-week field study of 383 dogs given Bravecto tablets, there were four adverse events reported that were considered to be possibly related to the drug (Rohdich et al, 2014). The dogs in this study remained at home and followed their normal routines, rather than being kept in controlled conditions. This makes it hard to determine if these presentations were caused by the drug or by another variable. However, the demographics of the dogs enrolled in the study were varied, so results can be applied to a wider population. For example, hair length included short, moderate and long, and living conditions included inside, outside and both. Meadows et al (2014) conducted a randomised blind field study in which 224 dogs were treated three times with fluralaner tablets. The dogs were observed for adverse drug reactions by detailed owner reports and regular clinic visits for 26 weeks. The adverse reactions reported were described as transient and mild. Blood and urine collected from the dogs at day 0, week 12, and week 26 were assessed for signs of any possible adverse drug effects; all results came back normal. Despite the presence of some drug-related adverse reactions, fluralaner was determined safe to use in dogs.

A multi-centre randomised study investigated the flea control efficacy of Bravecto spot-on in 224 cats. The cats were observed by their owners for 15 weeks to determine the safety of the product. The most common adverse drug reaction produced was vomiting (7.6%), followed by pruritus (5.4%). The researchers concluded that none of the reported drug reactions were severe and that fluralaner spot-on was safe for use in cats (Meadows et al, 2017). The NOAH datasheet for Bravecto spot-on shows that skin reactions are the most common adverse drug reaction for both cats and dogs. A number of other reactions have also been observed in cats (NOAH, 2017c).

Fipronil (Frontline)

Frontline (Merial Animal Health Ltd) spot-on for cats and dogs contains fipronil. This ectoparasiticide is applied topically, directly to the skin, once a month (Becskei et al, 2016b). Fipronil belongs to the phenylpyrazole family, which are potent antagonists for GABA-gated and glutamate-gated chloride channels in arthropods (Cole et al, 1993; Narahashi et al, 2010). This leads to inhibition of depolarisation, neuronal hyperactivity and death of the arthropods. Fipronil is lipophilic so it remains active if the animal gets wet (Beugnet and Franc, 2012). Fipronil (10% weight/volume) spot-on treatment was found to be 100% effective in eliminating adult *C. felis* on dogs for up to 29 days and <95% effective for 5 weeks (Young et al, 2004). Additionally, Frontline spot-on is >90% effective at 48 hours after *I. ricinus* challenge for up to 4 weeks (Bonneau et al, 2010). A single treatment of Frontline spot-on for cats is also successful in controlling feline cheyletiellosis (Scarampella et al, 2005). The laboratory and field studies that Pollmeier et al (2002) conducted, demonstrated that fipronil is an effective treatment and control of *Trichodectes canis* infestations on dogs. There is anecdotal evidence among veterinary professionals to suggest that Frontline is no longer effective, but this does not hold the same weight as field trials or laboratory tests.

Safety of Frontline

Of 178 dogs treated with Frontline spot-on in a field study, only one dog developed intense pruritus, while three dogs developed alopecia and crusts in the dorsal lumbo-sacral area (Rohdich et al, 2014). It was suggested that the primarily dermal nature of the adverse events might be expected as the treatment is topical. Another field study focused on cats, observed mild drooling and transient itching immediately after fipronil spot-on treatment (Geurden et al, 2017a). These signs ceased within a few minutes and it was stated that they were not unexpected events following a topical application to cats. The datasheet in the NOAH compendium states that drooling may occur as a result of licking the product, because of the solvents in it. Localised skin reactions at the application site were also reported, including erythema, alopecia, pruritus and scaling (NOAH, 2017d).

Imidacloprid (Advantage)

The active ingredient in Advantage (Bayer plc) spot-on treatment for cats, dogs and rabbits is imidacloprid, which is a neonicotinoid. It causes spastic paralysis in insects by binding to post-synaptic nicotinic acetylcholine receptors. The extended opening of sodium channels results in constant depolarisation of the neuron (Stanneck et al, 2012a). Imidacloprid is absorbed through the intersegmental membranes of the larval and adult cat flea (Mehlhorn et al, 1999). One group of researchers investigating the speed of efficacy of a number of different ectoparasiticides, infested cats and dogs with 100 unfed adult *Ctenocephalides felis* and counted the fleas following treatment with an allocated product (Schenker et al, 2003). Imidacloprid spot-on for cats proved to be 26.9% effective at reducing the adult cat flea burden 3 hours post-treatment and 82.8% at 8 hours post-treatment. The efficacy of imidacloprid spot-on for dogs was 22.2% at 3 hours post-treatment and 95.7% at 8 hours post-treatment.

A similar study also examined the speed of kill of imidacloprid, but re-infested the subjects every 7 days with 100 fleas (Everett et al, 2000). It was concluded that Advantage spot-on for dogs provides significant flea control in as little as 6 hours post-treatment. Moreover, despite Advantage spot-on being labelled as a product for monthly application, it provided 93.8% flea control at 24 hours after re-infestation at 41 days after treatment. In contrast, another study investigating imidacloprid found the long-term efficacy against fleas in cats to be much lower. Domestic short haired cats were infested with 25 adult *C. felis felis* and 25 adult *C. felis strongylus* 2 days before being treated with Advantage spot-on for cats (Franc and Yao, 2007). It demonstrated 100% efficacy against both sub-species 2 days after treatment, but this started to decrease for *C. felis felis* from the ninth day after treatment. By day 31, efficacy against *C. felis felis* was just 76%. These results confirm the need for monthly application of Advantage spot-on treatments for maximum flea prevention in cats.

Safety of Advantage

The NOAH compendium states that skin reactions can occur very rarely as adverse drug reactions to Advantage spot-on treatment. These include alopecia, erythema, pruritus and skin lesions. Other very rare adverse events in cats and dogs include excessive salivation and nervous signs including incoordination, tremors and depression. In dogs, in rare cases of overdose or treated fur being licked, nervous system disorders (lethargy, mydriasis, miosis, twitching, tremors and ataxia) can occur. There have been no drug–drug interactions observed in the field with other commonly used veterinary products (NOAH, 2017b). All recent studies in veterinary literature investigating Advantage spot-on for cats and dogs found no treatment-related adverse reactions. A significant example of this is an Italian field study of 3272 cats and dogs with natural *C. felis* infestations, treated with Advantage. There were no reactions at the application site and no reactions when used in conjunction with other drugs (Genchi et al, 2000).

Lufenuron (Program)

Program (Elanco Animal Health) contains lufenuron and is administered orally or as a subcutaneous injection (Beugnet and Franc, 2012). Lufenuron is a type of insect growth regulator (Rust and Hemsarth, 2017). As an inhibitor of chitin synthesis and deposition, lufenuron can be used to prevent reproduction of flea infestations in cats and dogs on account of its ovicidal and larvicidal properties (Dean et al, 1999; Zur and Elad, 2006). Chitin is a polysaccharide used for the formation of the exoskeleton of arthropods (DeBoer et al, 2003). Jacobs et al (2001) proposed that since lufenuron is not adulticidal, a simultaneous treatment may be required for the elimination of adult fleas in the early stages of treatment. An additional use of lufenuron is treatment of fungal infections in cats and dogs, as fungal cells walls contain chitin (Ben-Ziony and Arzi, 2000).

Maynard et al (2001) found that of 99 cats carrying a natural flea infestation, then receiving oral lufenuron suspension once a month for 6 months, 30% had zero fleas on day 30 compared to 71% on day 180. Another study, which was controlled, showed that flea counts on cats dosed with lufenuron tablets did not begin to decline until 59 days after treatment (Ritzhaupt et al, 2002). Of the sixteen cats treated with lufenuron in this study, four cats presented with hair loss and pruritus as a result of flea allergy dermatitis and required appropriate treatment. The findings of both of these studies support the recommendation of Jacobs et al (2001) that an additional adulticidal treatment for faster resolution of severe flea infestations is in the interests of the animal welfare.

Safety of Program

The datasheets in the NOAH compendium state that lufenuron is well tolerated and any adverse reactions are rare. The lufenuron injection for cats may cause short-lived lethargy or a mild reaction at the injection site. The datasheets for lufenuron oral suspension and tablets indicate that malaise, itching, gastrointestinal signs and nervous signs are possible adverse events. There are no known drug interactions with lufenuron (NOAH, 2017e). In a clinical trial to evaluate the safety of the 6-monthly Program injection for cats, the most common adverse reaction was pain or tenderness during injection. Other reactions included lumps at the injection site, vomiting, lethargy, diarrhoea and anorexia (Food and Drug Administration, 1998). A European field study

comparing lufenuron to another insect growth regulator for natural flea infestations on cats reported one adverse event. Out of the 99 cats given lufenuron oral suspension once a month for 6 months, signs of nausea were evident in just a single cat (Maynard et al, 2001).

Selamectin (Stronghold)

Selamectin is the active ingredient in Stronghold (Zoetis UK) spot-on for cats and dogs. It is a macrocyclic lactone active against a variety of ectoparasites and endoparasites of cats and dogs (Blot et al, 2003). Lethal paralysis of arthropods and nematodes is caused by chloride channel opening in peripheral nervous tissues (Krautmann et al, 2000). This review focuses solely on the ectoparasiticidal actions of the drug. A study investigating the pharmacokinetics of selamectin after topical application in dogs found that plasma drug concentrations were significantly higher in females and clearance was higher in males (Dupuy et al, 2004). The possible reasons for this gender difference, as described by Dupuy et al, include a sex-linked metabolic difference and a higher fat content in females acting as slow-release reservoir. Nonetheless, the minimum dose for selamectin is 6 mg/kg for cats and dogs of both genders (Fisher and Shanks, 2008).

Selamectin demonstrates ovicidal, larvicidal and adulticidal effects against cat fleas (McTier et al, 2000). Selamectin spot-on has demonstrated a 97.43% and 93.96% efficacy at reducing flea counts on dogs 14 and 30 days after treatment, respectively (Hayes et al, 2015). Everett et al (2000) determined that selamectin achieved 95.3% flea control on dogs, 24 hours after re-infestation with 100 adult *C. felis* 27 days post-treatment. In agreement with these findings, selamectin was found to be highly suited to prevent cats and dogs from experimentally induced environmental flea infestations (Shanks et al, 2000). Over the 3-month study, flea counts on the test subjects had reduced by >99% on day 14 post-treatment for dogs and day 44 for cats, when compared with the negative-control treatment, without the need for additional environmental control measures. All of these studies prove the ability of Stronghold spot-on to treat flea infestations for the length of the approved product labelling of one month. In addition, topical application of selamectin has proven 100% effective at eradicating infestations of the sucking louse, *Linognathus setosus*, 7 days after treatment (Gunnarsson et al, 2005). Naturally occurring infestations of sarcoptic mange and otodectic mange in cats and dogs can also be resolved with selamectin treatment (Six et al, 2000).

Safety of Stronghold

Stronghold spot-on has proven to be safe to use in both cats and dogs, including ivermectin-sensitive Collies (Bishop et al, 2000). The NOAH compendium states that neurological signs such as seizures have been reported very rarely after Stronghold spot-on application in cats and dogs. In cats, alopecia at the site of application and focal irritation have also been reported. These dermatological signs are usually mild and self-resolving (NOAH, 2017g). A series of randomised field studies compared the efficacy of selamectin to other positive controls for the treatment of naturally acquired sarcoptic and otodectic mange (Six et al, 2000). The positive controls were existing approved products at the time, such as Vet-Kem sponge-on wash (Sanofi Animal Health) for sarcoptic mange, and Otomite ear drops (Virbac) for otodectic mange. Overall, 236 dogs and 159 cats were treated with a selamectin spot-on formulation. The demographic for the pets involved in the study included ages ranging from 6 weeks to 16 years, a very large range of weights (0.8–61.7 kg for dogs and 0.5–8.2 kg for cats), and a mixture of males and females, pure-breeds and crossbreeds. Discolouration of the hair coat, localised to the application site of the spot-on, was observed in one dog. This was clearing up by the time of the final assessment on day 60 and there were no related skin lesions. This was the only treatment-related adverse event reported. Six et al (2016) also noted that the subjects were administered various concurrent medications throughout the studies, with no related adverse effects. These studies demonstrate the safety of selamectin for use in a wide variety of cats and dogs, alongside numerous other medications. In a field study, eleven dogs with a natural sucking louse infestation were treated with selamectin spot-on treatment and were observed for adverse reactions by owners and at clinic visits (Gunnarsson et al, 2005). One owner reported short-lived lethargy in their dog. As this was a very small-scale study, the frequency of any adverse events may be not be an accurate representation of the population.

Indoxacarb (Activyl)

Activyl (Virbac) spot-on solution for cats and dogs contains indoxacarb. It is a pro-insecticide from the oxadiazine class, bioactivated once inside the insect host by esterase and amidase enzymes (Wing et al, 2000). The active metabolite of indoxacarb is a powerful insect neuronal voltage-dependent sodium channel blocker (Lapied et al, 2001). A 2-month field investigation demonstrated that a monthly topical indoxacarb application is able to control flea populations in naturally heavily flea-infested cats and dogs, and their homes (Dryden et al, 2013a). A controlled laboratory study evaluating the efficacy of indoxacarb spot-on against *C. felis* on cats showed interruption of flea reproduction for at least 6 weeks after treatment (Dryden et al, 2013b). Flea egg production was almost eradicated, with the few eggs present showing reduced viability. Flea infestations were non-existent for 4 weeks after a single treatment and there was 99.6% efficacy after 6 weeks.

Dogs suffering with flea allergy dermatitis can be treated with indoxacarb, with no other concurrent treatment required. Clinical signs of flea allergy dermatitis were completely resolved in 87.5% of cases, with marked improvement in the remaining cases, in an Australian field study (Fisara et al, 2014). Armstrong et al (2015) evaluated the persistent flea control efficacy of topical Activyl. Dogs were infested with 100 adult *C. felis* 2 days before treatment and then once a week for 4 weeks. Flea counts were carried out in a thorough and systematic way to ensure reliability for all counts. The negative control group had large flea counts throughout the study, indicative of a consistently strong flea challenge. The indoxacarb-only treatment group demonstrated >99% flea control throughout the 30-day study. Bathing dogs with a medicated shampoo

every 2 weeks in combination with indoxacarb treatment did not significantly reduce the efficacy of flea control.

Safety of Activyl

The NOAH compendium datasheets for Activyl spot-on for cats and dogs provide a range of reported adverse drug reactionos (NOAH, 2017a). In cats, emesis and neurological signs such as incoordination, tremors, ataxia, convulsions, mydriasis and impaired vision have been reported in rare cases. Other very rare adverse drug reactions are also reported, which are reversible if supportive treatment is given. Furthermore, short-lived hypersalivation can occur rarely in both cats and dogs if they immediately lick the application site after treatment. Skin reactions (erythema, alopecia, pruritus and dermatitis) at the application site can occur in both cats and dogs. Some potential adverse drug reactions were detected in a 2-month study in which 32 dogs were given monthly indoxacarb treatment for natural flea infestations. These drug reactions, including vomiting, lethargy, inappetence and vocalisation, were reported on the first day of treatment (Dryden et al, 2013a).

Deltamethrin (Scalibor Protector Band)

Deltamethrin is from the pyrethroid chemical class. The Scalibor Protector Band (MSD Animal Health) is an adjustable collar for dogs which contains deltamethrin (NOAH, 2017f). Pyrethroids open sodium channels within insects to induce nerve depolarisation, leading to paralysis. However, their key advantage is that they act as a repellent to flying insects and ticks through irritating and neurotoxic actions (Beugnet and Franc, 2012). Cats are hypersensitive to pyrethroids as they lack the enzymes for their metabolism (Anadón et al, 2009). Results from a controlled Australian study suggested that the Scalibor Protector Band collar can take up to 2 weeks to achieve >95% efficacy against the paralysis tick, *I. holocyclus* (Webster et al, 2011). Laboratory tests showed that peak efficacy against infestations of *I. ricinus* and *R. sanguineus* is achieved after 1 week of use (Van Den Bos and Curtis, 2002). The slight delay for optimal efficacy in both of these reports is a result of the slow release and dispersal of deltamethrin from the collar through the hair and lipid layer of the skin around the whole body. For a 6-month period, the Scalibor Protector Band collar was >90% effective against *I. ricinus* and *R. sanguineus* (Van Den Bos and Curtis, 2002).

Franc and Cadiergues (1998) fitted dogs with a deltamethrin-impregnated collar and infested them with fleas at set intervals. Flea counts were performed 24 and 48 hours after each re-infestation, and then the fleas were removed. It was concluded that deltamethrin collars can control flea populations on dogs from 2 weeks after application, continuing until 150 days after application. Another study showed the protective flea efficacy of deltamethrin collars to be 66.7–83% for 170 days (Horak et al, 2012).

Safety of Scalibor Protector Band

The NOAH compendium of datasheets reported rare and very rare adverse reactions associated with the use of the Scalibor Protector Band for dogs. For example, localised or generalised skin reactions including alopecia, erythema and pruritus have been observed rarely. This skin irritation can be concurrent with altered behaviour such as lethargy or hyperactivity. Gastrointestinal signs and neuromuscular problems, such as ataxia and muscle tremors, have also been reported. It is suggested that removal of the collar will resolve any neuromuscular signs within 48 hours (NOAH, 2017f).

Non-chemical support measures

Environmental control of ectoparasites involves destroying their habitats, as well as those of any animals that may serve as alternative hosts in gardens (Blagburn and Dryden, 2009). Regular vacuuming of carpets and pet bedding areas can decrease flea egg numbers (Bitam et al, 2010). Vacuuming a 50 cm x 50 cm piece of carpet infested with 100 *C. felis* eggs for 10 seconds removed up to 80% of the eggs (Beck et al, 2004). Also, cats with frequent outdoor access have been shown to be more commonly infested with *Otodectes cynotis* and fleas, compared to cats with infrequent outdoor access (Beugnet et al, 2014). Limiting the outdoor access of a cat could be a measure to help reduce, but not eliminate, their risk of ectoparasite infestations. Furthermore, avoidance of heavily tick-infested areas and routine inspections of pets by their owners can help reduce the chance of tick-borne disease transmission.

Plant-derived products are a natural alternative to synthetic ectoparasiticides (George et al, 2014). For example, oils of citronella, cloves and lily of the valley can act as a repellent of the nymphs of *I. ricinus* for up to 8 hours, but their safety has not been proven (Thorsell et al, 2006). Fleas use visual and thermal cues to find a host, so flea traps with incandescent light bulbs can be used as a non-chemical method to help control or monitor flea infestations. A trap that uses intermittent light was found superior than one that uses continuous light to attract fleas (Müller et al, 2011). It has been speculated that the fleas perceive the intermittent light as a shadow of a passing host and that a green-yellow filter is more effective at attracting fleas than white light or any other filter (Dryden and Broce, 1993).

Problems associated with ectoparasiticide treatment

Many ectoparasite prophylaxis drugs do not eliminate the chance of parasites attaching and potentially spreading vector-borne diseases to the host. Numerous ectoparasiticides act systemically. For example, the action of fluralaner depends on the ticks ingesting the active compound during feeding, so they must start feeding from the host (Taenzler et al, 2015). Only a repellent drug such as deltamethrin prevents ticks from attaching and feeding. Other problems associated with the use of ectoparasiticides are described below.

Resistance

Resistance to insecticides can be challenging to assess, because of constant re-infestations by urban wildlife, infrequent use of treatment and environmental infestation (Dryden, 2010). Lack of owner compliance, vomiting of oral medications and bathing a topically treated pet can be other reasons for control failure (Payne et al, 2001). There is evidence to suggest that the cat flea has the potential to develop resistance to insecticides. Some

strains of *C. felis* have reduced susceptibility to fipronil (Payne et al, 2001). Two field strains of *C. felis* from the USA have showed a tolerance to five insecticides (Bossard et al, 2002). It has been advised that monitoring programmes are important to extend the longevity of current therapeutic agents against small animal ectoparasites (Rust, 2005).

Owner compliance

Lack of owner compliance is one of the most common explanations for ectoparasiticide treatment failure (Halos et al, 2014). A USA-based survey of Bravecto purchases found that only 13% of 559 dog owners purchased enough medication for a full year, despite most vets recommending all-year-round treatment (Lavan et al, 2017). The researchers speculated that the reasons for low compliance could include the belief that protection is not needed all year, the cost of treatment or forgetfulness. An 8-year study in a veterinary teaching hospital showed that out of 1271 dogs with available data, 74% were receiving flea and tick prevention measures (Gates and Nolan, 2010). Out of the dogs using treatment, only 61% had treatment all year round and 35% had treatment seasonally. In the same study, 138 cats were analysed and only 38% had been given an ectoparasiticide. Another survey, conducted at Lisbon University Small Animal Hospital, revealed that less than 30% of dogs were given year-round protection against the most common ectoparasites and canine vector-borne diseases (Matos et al, 2015). To improve owner compliance, awareness campaigns and educational programmes, alongside the improvement of vet-client relationships, are essential (Elsheikha, 2016).

Adverse drug reactions

Adverse drug reactions can be categorised into dose dependent (type A) or non-dose dependent (type B) reactions (Voie et al, 2012). Type A reactions are common, predictable and are caused by the pharmacological or toxic properties of the drug. Type B reactions are unpredictable, only happen to those with a certain predisposition, and can be sub-divided into two categories; idiosyncratic and immune-mediated (Schnyder and Pichler, 2009). The exact mechanisms of idiosyncratic drug reactions are unknown and their severity can vary between individuals (Shaw et al, 2010). It is thought that susceptibility to a reaction involves many genes, therefore developing models to better understand the mechanisms is challenging (Shenton et al, 2004). In the UK, serious adverse events must be reported directly to the Veterinary Medicines Directorate within 15 days, whereas non-serious adverse events must be reported in the next periodic safety update report (UK Government, 2016).

Drug–drug interactions

A drug–drug interaction can be defined as the altered pharmacological effect of one drug caused by the presence of a second drug. This can potentially result in adverse drug events (Ferdousi et al, 2017). Drug–drug interactions can be divided into pharmacokinetic and pharmacodynamic. The absorption, distribution, metabolism or excretion of a drug is altered in a pharmacokinetic interaction (Palleria et al, 2013). Whereas pharmacodynamic interactions occur when the concentration of the drug is not changed, but the effect of a drug is altered through action at the target site (Lin et al, 2010). Pharmacokinetic drug–drug interactions are a significant topic in veterinary medicine, as multidrug therapy is commonly used in small animal practice and can potentially result in fatal or adverse effects (Sasaki and Shimoda, 2015). A well-documented example of a drug–drug interaction is the interaction between ketoconazole and ciclosporin. Ketoconazole, an anti-fungal, can increase blood concentrations of ciclosporin, an immunosuppressant, by interacting with the enzyme pathway involved in the biotransformation of ciclosporin (O'Neill et al, 2004).

Recommendations to pet owners and vets

Dermatological adverse drug reactions threaten the health and welfare of an animal and can cause concern for the owner. This concern can be significant in the breeding and showing community, where the external appearance of an animal can be crucial to their success. For such clients, communicating the possibility of adverse drug reactions is imperative, which will potentially lead to the selection of a product that is less likely to cause dermatological reactions. Many gastrointestinal and neurological reactions can be a result of the companion animal ingesting the product by licking their fur, the likelihood of which can be increased by applying the product at an inappropriate site. To avoid this, effective communication with the owner, describing proper application, alongside reading the product information is essential. Similarly, administration of a correctly prescribed product and dose is vital for the safety of companion animals. For example, confusion between products for canines and felines can lead to an overdose and have fatal consequences for cats (Malik et al, 2010).

Conclusions

Adverse drug reactions can occur in cats and dogs and are associated with several therapeutic classes of ectoparasiticide drugs. Documenting information about each case of an adverse reaction to an ectoparasiticide, could provide vital information about the susceptibility of companion animals to certain reactions; for example a particular breed, age, gender or weight could have a predisposition to having an adverse reaction to a certain drug. This would allow both clinicians and owners to be more prepared for such an event. The authors strongly recommend further work to address procedures for the reporting of adverse drug reactions in small animal practice. It is necessary to understand if and how such reactions may be prevented. The development of standardised ways in which types of adverse drug reactions and the drugs contributing to these are reported in clinical observational studies, would enable better comparison between studies performed across different animals and settings. Finally, owners and practitioners should be made aware of the likelihood and potential severity of possible adverse reactions associated with any drug, in the interests of animal welfare.

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