Dirofilaria immitis and D. repens in dog and cat and human infections

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Epidemiology and prevention of *Dirofilaria* infections in dogs and cats

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Heartworm infection (*Dirofilaria immitis*)

*Dirofilaria immitis* is a parasite that can be potentially fatal to a variety of animal species. Dirofilariosis, however, is a fully preventable disease due to the availability of highly effective preventive drugs that are safe, effective, convenient and easy to administer. According to the recently published American Heartworm Society guidelines, all animals that are at risk for contracting the disease should routinely receive heartworm preventive medications (Nelson et al., 2005a,b).

Chemoprophylactic drugs for heartworm infection fall into two basic classes, the macrocyclic lactones or macrolides (avermectins and milbemycins) and diethylcarbamazine (DEC). In heartworm-endemic areas, puppies and kittens that are born during the transmission season should be given their first dose of macrocyclic lactones between 2 to 8 weeks of age and 6 to 8 weeks of age, respectively. The required daily administration of DEC is inconvenient, more than one missed dose can result in a breakdown in protection and the overall prevention program is difficult to manage. The use of DEC is fairly limited in the United States and the drug is no longer available in Europe.

The present chapter will briefly review current information on the epidemiology of *D. immitis* infections in dogs and cats and the use of macrocyclic lactones in the prevention of heartworm infection, as well as their effect on other important gastrointestinal nematode parasites.

Epidemiology

More than 70 species of mosquitoes have been shown to be capable of developing microfilariae (first stage larvae) to the infective, third-stage larvae (L3), but fewer than a dozen of these species are believed to be major vectors (Otto et al., 1981). Although the susceptibility of different geographical strains may vary, the likelihood of the presence of at least one susceptible vector species in a geographic area that is conducive to the propagation of mosquitoes is high, and once the ubiquitous heartworm parasite is introduced into an area, its transmission is virtually insured.

Many countries are now endemic for heartworm infection. Furthermore, in spite of efforts aimed at prevention and control, particularly in dogs, infection appears to be spreading into areas previously considered to be free of the disease (Genchi et al., 2005). The prevalence and distribution is better known for dogs, but gradually more information on the frequency of diagnosis of infection in cats is becoming available. It is now generally accepted that heartworm disease may occur in cats in any area where dogs are infected (Genchi et al., 1992b, 1998; Guerrero et al., 1992b; McCall et al., 1994; Kramer and Genchi, 2002) but the geographical distribution and level of infection are less predictable in cats than in dogs. In highly endemic areas, with sufficient rainfall, essentially every unprotected dog becomes infected (McTier et al., 1992a). In contrast to dogs, about 75% of cats can be infected experimentally with *D. immitis* L3.
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(McCall et al., 1992). However, the prevalence rate of natural infections in cats is between 5% and 20% of that for dogs in the same geographical area (Ryan and Newcomb, 1995).

Cats with naturally acquired infections usually harbor fewer adult worms than dogs. Because of their small body size and exaggerated pulmonary vascular and parenchymal response to infection, cats with low worm burden can be considered to be relatively heavily infected in terms of parasite biomass (Genchi et al., 1998). Microfilaremia, when present, is low and transient, even in cats with experimentally induced infections. Mosquitoes fed on heartworm microfilaremic cats develop L3, which are capable of producing an infection in dogs (Donhaoe, 1975), but circulating microfilariae are seldom found in cats. Thus, cats generally become infected via mosquitoes that have fed on microfilaremic dogs.

It is not currently possible to determine which cats are resistant to heartworm infection and which are susceptible and will permit the infection to develop to the adult stage. Such a distinction between resistant and susceptible animals would require constant monitoring at very high costs.

Furthermore, environmental measures taken to reduce the risk of infection seem to be of little consequence in the cat. In fact, keeping animals indoors, one of the most important measures in reducing infection rates in dogs, seems to be ineffective in protecting cats from disease. Outdoor cats and strays who are seemingly exposed to high numbers of bites from infective mosquitoes may be able to mount an effective immune response that could be partially protective (Dillon et al., 1996; Prieto et al., 2001); however, studies to determine levels of susceptibility have not been performed. For indoor cats, it seems that even one encounter with an infective vector may lead to the development of a large proportion of transmitted larvae to the adult stage, causing severe illness (Genchi et al., 1992a). It has recently been reported that between 9 and 27 percent of cats were seropositive for *D. immitis* in northern Italy, 19 percent of which were apartment-dwelling cats (Kramer and Genchi, 2002).

Chemoprophylactic treatment, therefore, is a viable option for cats residing in any area where heartworm is considered endemic in dogs, even cats living more sheltered lives. As suggested by Atkins (1997), it seems rational to recommend chemoprophylaxis for feline heartworm infection, given that the disease has a higher incidence than both Feline Leukemia Virus (FeLV) and Feline Immunodeficiency Virus (FIV), infections for which vaccination protocols are increasingly advocated.

Heartworm transmission to dogs and cats is influenced by several well-known epidemiological factors, among the most important of which is environmental heat. Development of *D. immitis* to L3 in mosquitoes occurs at a rate that is dependent on ambient temperature, and development may not occur at a threshold temperature of about 14 °C (Fortin and Slocombe, 1981). The effects of heat on larval development is assumed to be cumulative and may be calculated in terms of degree-days above the developmental threshold, or heartworm development units (HDU). One model of heartworm
seasonality assumes a requirement of 130 HDU (°C) for complete development and a maximum life expectancy of 30 days for common vector mosquitoes (Slocombe et al., 1989). Using this laboratory-derived model, which requires numerous inherent assumptions and was designed to study only the influence of macroenvironmental temperature on the heartworm development period, investigators have predicted the seasonal limits of transmission in Canada (Slocombe et al., 1995), the USA (Knight and Lok, 1995) and Europe (Genchi et al., 2005) and formulated recommendations for timing of heartworm chemoprophylaxis and scheduling of diagnostic testing. While these model-based predictions are academically appealing, they ignore several potentially important factors, such as influence of microclimate and the unique biological habits and adaptations of the numerous mosquito vectors, on larval development.

Prevalence

North America

Heartworm infection in dogs has now been diagnosed in all of the 50 states of the USA. Although transmission of infection has not been clearly documented for Alaska, the disease is considered to be endemic in all of the remaining 49 states. Heartworm is enzootic along the Atlantic Seaboard and Gulf Coast areas, with the southeastern states generally showing the highest prevalence values. Infection continues to be diagnosed at a high frequency in the Mississippi River basin and in states along the Ohio and Missouri Rivers. New foci have been detected in northern California and Oregon, and autochthonous infections in dogs in the states of Wyoming, Utah, Idaho, and Washington have been documented in recent years (Zimmerman et al., 1992).

There is a high probability that the introduction of the tree-hole breeding mosquito, *Aedes sierrensis*, in Salt Lake City, Utah, during the past decade or so is associated with the establishment of enzootic heartworm transmission in the area (Scoles and Dickson, 1995). The tiger mosquito, *A. albopictus*, a known vector of heartworm in Japan, has spread rapidly throughout much of the USA and Europe since it was introduced from Asia in 1985. It breeds mainly in piles of discarded tires and is spread within the country by movement of tires from place to place. This mosquito readily feeds on dogs and other mammals, and laboratory strains have shown it to be an excellent host for *D. immitis*.

Two recent surveys conducted by Merial in cooperation with the American Heartworm Society showed that the number of canine heartworm cases diagnosed in the US were close to a quarter of a million. The first survey conducted in 2002 requesting diagnostic data for 2001 had the participation of 15,366 clinics which reported diagnosing heartworm infections in 244,291 dogs. The second survey conducted in 2005 reviewing data for 2004 had the participation of 12,173 clinics (out of a total of 25,000), which reported 250,000 cases of canine heartworm infections diagnosed that year (Guerrero et al., 2006). Interestingly, 8,800 of the responders in the second
survey had also responded in the first survey. Analyzing the data obtained in the clinics that participated in both surveys the following was seen: number of canine heartworm cases decreased in 17 states, in 3 states the numbers were the same and in 30 states plus Washington, DC the number of cases increased. Nationally, the reported positive cases of heartworm infections in dogs increased slightly in those clinics reporting in both 2002 and 2005.

In a parallel study, the national prevalence of heartworm infections in dogs was performed by evaluating medical records of more than 500 Banfield Pet Hospitals that see approximately 80,000 pets on a weekly basis. Data collected from January 1st 2002 to December 31st 2005 was evaluated. Results of this study show that 1.46% of the 871,839 dogs examined tested positive for circulating antigen of *D. immitis*. Based on this data, the estimates of pet dogs in the USA and the proportion of them probably on heartworm prevention, the investigators (Apotheker et al., 2006) estimated that 509,932 dogs in the USA had heartworm infections, a figure that is almost exactly double the number of cases reported in the Merial-AHS surveys of 2002 and 2005. Keep in mind that in the 2005 Merial-AHS survey close to half of the total number of Companion animal clinics in the USA responded to the survey.

In Canada, the overall canine prevalence rate is 0.24% (Slocombe, 1992). Prevalence is higher (8.4%) in endemic areas of southwestern Ontario. The most significant reports of heartworm infections in British Columbia are from the Okanagan Valley area, which represents a classic instance of recent introduction of the parasite and a resulting local pocket of infection (Zimmerman et al., 1992). Hunters, in previous years, had transported hunting dogs from Texas to this area, setting up new foci of infection.

**South America**

The prevalence and spread of heartworm infection in South America has been recently reviewed by Labarthe and Guerrero (2005). Surveys indicate that heartworm is endemic in several countries of South America. In Brazil, the overall prevalence of canine heartworm infection in the state of Rio de Janeiro was 21.3% (Guerrero et al., 1992a), with the highest rate for dogs in the northern beaches (49%), followed by dogs from the mountain towns near the cities of Rio de Janeiro (27.4%) and Niteroi (26.4%). The rate in the suburbs of Rio de Janeiro was around 53% (Labarte et al., 1992). Labarthe and co-workers (1997 a,b) confirmed and extended these findings, and also reported heartworm infection in random-source cats in the city. Alves and co-workers (1999) found a prevalence rate, as determined by necropsy of dogs, in the city of Recife in northeastern Brazil of 2.3%. In the same state (Pernambuco), prevalence in dogs on Itamaracá Island was found to be as high as 43%. Labarthe (1997) reviewed the literature on prevalence in Brazil and found reports of prevalence rates as high as 45% in the state of São Paulo. In Argentina, endemic areas have been identified, with prevalence in dogs ranging from 5.0% in the greater Buenos Aires area to 34.2% in the northeastern province of Formosa (Guerrero et al., 1992a). A rate of
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10.9% was recorded for Corrientes. More recently, Peteta and co-workers (1998) reported a prevalence, determined by microfilarial and antigen testing, of 13.6% for dogs in Villa La Nàta, which is located near the Parana Delta and surrounded by the Lujan River and Villanueva and LaRioja Channels in the Tigre district of the province of Buenos Aires. In Argentina the prevalence ranges from 0% to 71% (Vezzani et al., 2006). In Venezuela, examination of canine blood samples submitted to the School of Veterinary Medicine, Central University of Venezuela in Aragua, revealed that 2.3% were positive for microfilariae of *D. immitis* (Perez and Arlett, 1998). Recent studies performed in Lima, Peru, reported 4.35% of the blood samples from 140 randomly selected dogs were positive for circulating antigen of *D. immitis*. These samples were examined by the ELISA Snap 3Dx test (Gonzales, 2002).

Central America and the Caribbean

Kozek and co-workers (1995) reviewed the prevalence of canine filariae in the Caribbean islands and conducted a thorough epidemiological survey in Puerto Rico. Prevalence values for heartworm infection in Puerto Rico ranged from 3.1% to 20.4%, with the highest rate recorded for the city of Ponce, on the southern coast. In Cuba, prevalence for Havana ranged from 7% to 19% and from 37% to 65% on the Isla de Juventud. For Curacão, it ranged from 9% to 11% and was 53% for the Grand Bahamas and 18% for the Dominican Republic.

In a survey covering 15 cities in Mexico (Guerrero et al., 1992a), the overall heartworm prevalence in dogs was found to be 7.5%, with the highest rates (20-42%) observed for dogs from the Gulf Coast cities of Tuxpan, Tampico, and Ciudad Madero.

Australia

Heartworm infection is enzootic along the northern coastal areas of Western Australia and the eastern states of Queensland, New South Wales, and Victoria, where prevalence rates generally mimic those for the southeastern states of the USA. The prevalence of heartworm infection in dogs in Sydney was as high as 30% in the late 1980s, and cats were also found to be infected (Kendall et al., 1991). More recently, the rate for dogs in this area was reported to be only 11.4% (Bidgood and Collins, 1996).

Asia and the South Pacific

Heartworm disease is well established in most of the Islands of the Pacific and in many countries of Asia, but survey results are not readily available for every country. A prevalence of 11.3% for dogs from the Fars province of Iran has been reported (Jafari et al., 1996). Heartworm is enzootic on the islands of Japan, where the disease is well known and prevalence is well documented. A survey conducted on stray dogs and cats in the Kanto region of Japan in 1985 revealed a prevalence rate of 59% for dogs and 2% for cats (Tanaka et al., 1985). More recently, Roncalli and co-workers (1998) reported that prevalence rates for feline heartworm infection in Japan ranges from 0.5% to 9.5% in stray cats and
from 3.0% to 5.2% in house cats. A survey of German shepherds in five areas of South Korea revealed an overall prevalence of 28.3%, by an antigen test (Lee et al., 1996). Prevalence was highest in Hoengsong-gun (84.4%), while Yechon-gun and Chungwon-gun areas had rates of 20.0% and 14.3%, respectively. None of the dogs in the Kimhae-shi and Kwanju areas was positive. Kuo and co-workers (1995) reported a 53.8% prevalence for dogs in the Taipei province of Taiwan, and Wu and Fan (2003) an overall prevalence of 57% in stray dogs in Taiwan.

**Europe**

The prevalence and spread of heartworm infection in Europe has been comprehensively reviewed by Genchi and co-workers (2005). The disease is diagnosed mainly in the southern European countries of Spain, Italy, Portugal, and France, with scattered reports from Greece, Turkey, and some Eastern European countries. An increasing number of cases are now being diagnosed in northern countries such as Austria, Germany, and The Netherlands in dogs that were either imported from the Mediterranean area or had accompanied their owners to the area. One possible exception is a heartworm-positive dog from the Canton of Tessin (Switzerland), which appears to have acquired an autochthonous infection.

For Europe, the area of highest prevalence values for dogs and cats is along the Po River Valley in northern Italy. The prevalence rate for cats in this area is high (up to 24%), and the rate for dogs ranges from 35% to 80% in animals not treated with preventive drugs. The disease has recently spread northward into the provinces of Friuli-Venezia-Giulia. Furthermore, the spreading of *A. albopictus* in Italy and the evidence that this mosquito species can act as a natural vector for *D. immitis* can enhance the risk of transmission from animals to humans, considering the aggressive anthropophyllic behavior of the species (30-48 bites/hour) (Cancrini et al., 2003).

The highest rates for dogs in Spain are reported for the southern provinces of Huelva (37%), Cadiz (12%), and Badajoz (8%) (Guerrero et al., 1992 a). During the past few years, *D. immitis* infection appears to be spreading into other regions of Cataluña (Catalonia). A recent survey of Barcelona showed that 12.8% of the dogs were infected. The Canary Islands of Tenerife (20.0%) and Las Palmas (36.0%) are highly endemic, and a recent report suggests that about 59% of the dogs on Gran Canaria Island are infected with heartworms. In Portugal, infection is diagnosed mainly in the southern regions, with prevalence values ranging from 12% (Algarve) to 30% (Island of Madeira). Although limited survey data are available, prevalence values for dogs range from 2% to 17% for Slovenia, Bulgaria, Greece, and Turkey and up to 65% for Romania, and some of these areas are considered to be endemic. In Croatia, canine heartworm infection has been reported from Istrian peninsula (about 16% prevalence) and the suitest regions (Dubrovnik; about 8%) (Živičnjak et al., 2006).

**Africa**

Heartworm is found in dogs from various regions of Africa, but no infor-
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Information is available regarding infections in cats. Infection in dogs appears to be common throughout western Africa and in eastern parts, extending from the Republic of South Africa and Mozambique (Schwan and Durand, 2002) to the Republic of Sudan. Matola (1991) reported a prevalence of 10.2% for dogs in Tanzania.

Chemoprophylactic treatment of canine heartworm disease

Since the discovery of ivermectin and the initial description of activity against developmental stages of *D. immitis* a large number of publications have appeared reporting on their attributes.

Monthly oral administrations of ivermectin at 6-12 mcg/kg, milbemycin oxime at 500-999 mcg/kg, or oral moxidectin at 3 mcg/kg provide effective protection against heartworm infections in dogs.

An ivermectin/pyrantel chewable formulation is also available in Europe and in the United States to expand the indications to include treatment and control of certain gastrointestinal parasites, including *Toxocara canis*, *Toxascaris leonina*, *Ancylostoma caninum* and *A. braziliense*. Milbemycin oxime at the recommended dose for heartworm prophylaxis is also effective against *T. canis*, *T. leonina*, *A. caninum* and *T. vulpis*. Treatment with any one of these macrolide compounds should begin within a month after the beginning of the transmission season and the final dose should be administered within one month after the end of mosquito activity although, at present time the most accepted recommendation is to treat year-round (Nelson et al., 2005b). All three drugs have a wide range of efficacy, which allows them to be administered every 30 days. This provides a safeguard in the case of omission or delay of a monthly treatment, or when the chemoprophylactic history cannot be verified. Ivermectin and milbemycin oxime have both been found to provide a high degree of protection when administered on a regular basis, beginning 3 months after infection. In fact, monthly treatment with ivermectin over a one-year period has been shown to be >95 percent effective in preventing development of *D. immitis* larvae that were 4 months old; however, under the same conditions, milbemycin oxime was only 41.5 to 49.3 percent effective as a clinical prophylactic agent (McCall et al., 1992). This retroactive or “reachback” effect has not been reported for moxidectin, although products with this compound do have a label claim for efficacy of 2 months duration. This so-called “safe net” or “reachback” effect of macrocyclic lactones is very useful to compensate for missed or delayed treatments, but should not be considered as justification to modify the recommended monthly interval for treatment.

A newly developed avermectin, selamectin, has recently been approved in Europe and in the United States for the prevention of heartworm infections in dogs and cats. The drug was also 100% effective in preventing the development of heartworm infection in dogs when administered as a single topical dose of 3 or 6 mg/kg given at 30 or 45 days after inoculation with L3 or a single topical dose of 6 mg/kg given 60 days PI (Clemence et al., 2000; McTier
et al., 2000; Dzimianski et al., 2001; McCall et al., 2001). The drug was also safe when given to dogs and cats with existing heartworm infections. There are several important characteristics unique to selamectin: the drug is given as a topical formulation, thereby avoiding problems associated with oral administration. At the dose recommended for heartworm prevention in dogs and cats (6 mg/kg) selamectin is also effective in preventing and controlling flea infestations (*Ctenocephalides felis*) and for treating and controlling ear mites (*Otodectes cynotis*) and biting lice (*Trichodectes canis* and *Felicola subrostratus*) in dogs and cats; sarcoptic mange in dogs (*Sarcoptes scabiei*); and hookworm (*Ancylostoma* spp) and roundworm (*Toxocara* spp) in both dogs and cats.

An injectable formulation of moxidectin to be solely utilized by veterinarians in dogs for prevention of heartworm infections is sold in Italy and Australia. The commercial formulation (moxidectin sustained release injectable for dogs) has been approved for use in dogs six months of age and older, but not growing dogs. It is able to protect dogs for an entire heartworm transmission season (Genchi et al., 2002) and also treats infections with *A. caninum*.

**Chemoprophylactic treatment of feline heartworm disease**

Although the general guidelines and criteria for the use of preventive drugs in dogs may be generally applied to heartworm infection in cats, several specific features of feline heartworm disease must first be considered when choosing the correct prevention regimen. *D. immitis* infection in cats can cause an unpredictable, and often fatal, disease. Cats are known to be susceptible hosts for heartworm, but are extremely resistant to infection (Genchi et al., 1992a; McCall et al., 1992).

Preventive treatment in the cat follows the same regimen established for
the dog, i.e., monthly dosing should begin within one month from the start of the transmission season and the last dose should be given within one month from the end of the risk period. Ivermectin is marketed for use as a prophylactic agent in cats given monthly at the dose of 24 mcg/kg (McTier et al., 1992b). This oral dosage is also highly effective for treatment and control of *A. tubaeforme* and *A. braziliense*. The oral chewable formulation of ivermectin has been found to be 100 percent effective in preventing development of *D. immitis* larvae when administered 30 or 45 days after challenge with infective larvae.

Furthermore, McCall and co-workers (2000, unpublished data) demonstrated that the recommended prophylactic dosage of ivermectin administered monthly for a maximum of 12 months was 66.5 percent effective in clearing 7-month-old *D. immitis* that had been transplanted from an infected dog. A dramatic decrease in circulating antigen levels also was detected in ivermectin-treated cats. These findings are highly noteworthy for the cat veterinarian since adulticide treatments are not considered a viable option for cats. Milbemycin oxime is also known to be effective in cats for heartworm prophylaxis at a rate of 2 mg/kg (Genchi et al., 2004). In Europe, milbemycin oxime is available in combination with praziquantel (5 mg/kg) and the product is efficacious for preventing heartworm infection and for the treatment and control of *A. tubaeforme*, *T. cati*, *Felicola subrostratus* and *O. cynotis* (Guerrero et al., 2002).

As with the dog, pre-treatment testing is advisable in the cat, utilizing both an antibody and an antigen test for cats, to verify the absence of *D. immitis* infection; however, it is not mandatory. Retesting of cats should be considered after the first season of preventive treatment and is advisable at the beginning of each new transmission season before preventive therapy is to be initiated, unless the clinician has wisely chosen to utilize chemoprophylaxis year-round. The longer life cycle of the parasite in the cat, as well as the difficulty in accurately diagnosing infection, increase the risk of inadvertently treating an infected animal; however, based on data obtained by McCall et al. (2000, unpublished data), monthly administration of preventive drugs to cats infected with adult worms did not precipitate any negative reactions.

### Subcutaneous filarial infection

(*Dirofilaria repens*)

As for heartworm infections, subcutaneous filariosis can be safely and effectively prevented by chemoprophylactic treatment of both in dogs and cats.

Although the disease is less severe than heartworm infection and dogs can show cutaneous disorders of different severity, such as pruritus, dermal swelling and subcutaneous nodules containing the parasites (Baneth et al., 2002; Bredal et al., 1998), very severe infec-
tions have been reported (Restani et al., 1962; Mandelli and Mantovani, 1966), with allergic reactions probably due to microfilariae. However, the main concern about this *Dirofilaria* species is its ability to cause infections in humans in Europe. The number of zoonotic infections has dramatically increased in the last few decades (Pampiglione et al., 1995) and the infection now can be included in the list of emerging zoonoses (Pampiglione et al., 2001). The infection is spreading in many southern (Giannetto et al., 1997) and eastern European countries (Mazurkevich et al., 2004; Fok, 2007), probably as a consequence of the movement of infected dogs and global warming that increase the transmission season. Recently, Živičnjak et al. (2006) reported a prevalence ranging from 7-18% in dogs from several regions of Croatia. Cats, as well as dogs can be infected, but the prevalence seems quite low (0.2-0.5%; Genchi et al., 1993).

Ivermectin, selamectin and moxidectin (both tablets and subcutaneous injectable) have been found to be effective in preventing this subcutaneous infection in dogs naturally exposed to infective mosquitoes, by treating monthly (oral formulations) or once a year (moxidectin injectable formulation) and at the same doses that are effective against *D. immitis* (Marconcini et al., 1993; Genchi et al., 2002c; Rossi et al., 2002, 2004).

**Domestic ferrets**

The domestic ferret (*Mustela putorius furo*) has been reported to be susceptible to naturally acquired and experimentally induced infections of *D. immitis* (McCall, 1998). Laboratory studies have shown the ferret to be highly susceptible, with infection and recovery rates similar to those achieved in the dog and higher than those seen in cats (Supakorndej et al., 1994). The life span of adult heartworms in ferrets is thought to cover the entire life time of the ferret. Heartworms are somewhat smaller in ferrets than in dogs, with mean lengths of male and female worms recovered from the heart and associated vessels of 118 mm and 144 mm, respectively, 140 days after infection (Supakorndej et al., 1994).

Microfilaremia is characteristically of low concentration and transient in nature, similar to that seen in heartworm-infected cats. A definitive diagnosis can be made from ELISA-based antigen tests, echocardiography, and angiography, but suggestive radiographic findings require additional supportive information to confirm a tentative diagnosis (McCall, 1998; Sasai et al., 2000). Clinical signs upon presentation include lethargy, inappetence, exercise intolerance, pleura effusion, cyanosis and dyspnea (Antinoff, 2001).

Supakorndej and co-workers (2001) found that adulticide treatment of infected ferrets with melarsomine dihydrochloride enhanced cardiomegaly and alveolar infiltrates and increased the severity of interstitial disease. The drug at the dosage of 3.25 mg/kg was equally effective (80.6-83.3%) when given twice, 24 hours apart or one injection followed one month later by 2 injections, 24 hours apart, but several animals in the treated and control groups died during the study. Prevention has been shown to be
effective with currently used canine prophylactic compounds such as monthly treatment with ivermectin at 6 mcg/kg (McCall, 1998) or cat chewable ivermectin formulation (24 mcg/kg) (Kemmerer, 1998), but effective treatment of adult heartworms in ferrets has not yet been confirmed by controlled studies. There is currently no approved drug for prevention or treatment of *D. immitis* in ferrets.

**Guideline for the chemoprophylactic treatment of *Dirofilaria* infections in dogs**

1. Test the dog for circulating microfilariae (*D. immitis* and *D. repens*) and adult female antigens (*D. immitis*) when the preventive treatment is administered for the first time. Testing cats is not necessary but it is advised; drugs are safe even in cats with patent infection.

2. When a ≥ 1 year-old dog with an unknown history, living in an endemic area (risk area) is prophylactically treated for the first time, check for microfilariae and antigen before starting treatment and recheck after 6 months to exclude a possible pre-patent infection.

3. Retesting should always be carried out after the first season of preventive treatment and must include testing for circulating antigens as well as for microfilariae. It is also advisable to repeat testing at the beginning of each transmission season, before the start of treatment in order to exclude possible infections due to poor owner compliance or to verify that there was no pre-existing infection. In endemic areas where year-round treatments are utilized, yearly testing is recommended.

4. Treatment must be given monthly at the recommended dosage, but for moxidectin in the injectable formulation, one injection is able to protect dogs against *Dirofilaria* infection for at least six months. The commercial formulations are sold at dosages that are able to cover different ranges of body weight. The minimum effective dosage of macrocyclic lactones for prevention of *Dirofilaria* infection in dogs and cats and the indications against other parasites are shown in the table below.

<table>
<thead>
<tr>
<th>ML</th>
<th>Presentation</th>
<th>Species</th>
<th>Dose</th>
<th>Indications</th>
<th>Minimum age of treatment</th>
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<tr>
<td>IVM</td>
<td>Tablets/chewables</td>
<td>Dog</td>
<td>6 mcg/kg</td>
<td>Di, Dr</td>
<td>6 weeks</td>
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<tr>
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<td>Chewables</td>
<td>Cat</td>
<td>24 mcg/kg</td>
<td>Di, At, Ab</td>
<td>6 weeks</td>
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<tr>
<td>IVM/PYR</td>
<td>Chewables</td>
<td>Dog</td>
<td>6 mcg/kg</td>
<td>Dog: Di, Dr, Tc, Tl, Ac, Us</td>
<td>6 weeks</td>
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<td>Flavour tablets</td>
<td>Dog</td>
<td>0.5 mg/kg</td>
<td>Di, Tc, Tl, Ac, Tv 2 weeks or 0.5 kg</td>
<td>6 weeks</td>
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<tr>
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<td>Tablets</td>
<td>Dog</td>
<td>0.5 mg/kg</td>
<td>Di, Tc, Tl, Ac, Tv 6 weeks</td>
<td>Dc, Tae, Eg,Ms</td>
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<tr>
<td>MBO/LFN</td>
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<td>Cat</td>
<td>2 mg/kg</td>
<td>Di, Tct, At, Dc, Tae, Em</td>
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<table>
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<tr>
<th>ML</th>
<th>Presentation</th>
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<td>0.17 mg/kg</td>
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<td>Topical</td>
<td>Dog</td>
<td>6 mg/kg</td>
<td>Di, Dr, Tc, Cf, Ss, 6 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cat</td>
<td>6 mg/kg</td>
<td>Oc, Trc</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Di, Tct, At, Cf, Oc, Fs</td>
<td></td>
</tr>
</tbody>
</table>

Note: All of the compounds are intended for monthly administration except moxidectin injectable.

VM: ivermectin
PYR: pyrantel pamoate
MBO: milbemycine oxime
MOX: moxidectin
SLM: selamectin

Species:
- Di: *Dirofilaria immitis*
- Dr: *D. repens*
- Ac: *Ancylostoma caninum*
- At: *A. tubaeforme*
- Ab: *A. braziliense*
- Tc: *Toxocara canis*
- Tct: *T. cati*
- Us: *Uncinaria stenocephala*
- Tv: *Trichuris vulpis*
- Dc: *Dipylidium caninum*
- Ms: *Mesocestoides sp*
- Tae: *Taenia spp*
- Eg: *Echinococcus granulosus*
- Em: *Echinococcus multilocularis*
- Cf: *Ctenocephalides felis*
- Trc: *Trichodectes canis*
- Fs: *Felicola subrostrata*
- Oc: *Otodectes cynotis*
- Ss: *Sarcoptes scabiei*

References


Peteta L, Sigal G, Ribicich M, Rosa A, Perez Tort


