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Experience in the Ivermectin Treatment of Internal Parasites in Zoo and Captive Wild Animals: A Review



Ivermectin-Behandlung von Endoparasiten bei Wildtieren in Menschenobhut: Eine Übersicht

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Abstract

The selection and the use of antiparasitic remedies in the animals in zoological gardens and those bred in captivity present one of the challenges to the wildlife veterinarians. The latter have to be flexible enough in the choice of medicines and schemes of treatment of the animals they take care of. The present study is aimed at adding more information in that respect. A number of cases of ivermectin treating of mammals, birds, reptiles, amphibians and fish bred in captivity are presented in it. The tolerance to the drug in the different animals, species of the parasites influenced by it, dosages, schemes of applying and some other peculiarities in the system animals – diseases – anthelmintic treatments are discussed.

Keywords: Anthelmintic treatment; Captive wild animals; Ivermectin; Wildlife; Zoos

Introduction

Breeding animals in limited space as zoological gardens, rehabilitation centers, farms, reserves and others is characterized with the corresponding specificity of the diseases affecting them, including parasitoses. The amassing of a great number of animals often uprooted

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out of the natural habitat predisposes for a massive spread parasitoses amidst them. In a number of cases, for example in zoos, infections of animals with untypical parasites have been observed which have been acquired due to the close direct or indirect contact with other animal species. Often it is difficult to eliminate parasitic infection in captive animals because of confinement, changed environmental conditions and the movement of keepers from one enclosure to another. Hence attempts should be made to keep the parasite load low. For this, regular examination of fecal samples, assessment of parasitic load and administration of appropriate medicines is warranted at regular intervals (Singh, Gupta, Singla, Singh, & Sharma, 2006). The choice and use of antiparasitic drugs however are arranged among the challenges to wildlife veterinarians. In a great part of the cases the medicines on the market are designed for domestic animals and they should be adapted as to dosage and ways of application which is accompanied by the corresponding risks. On the other hand the continued use of one and the same antiparasitic remedies would lead to the emergence of resistance to them in the animals treated. These factors enforce the wildlife veterinarians to be flexible enough in the choice of medicines and schemes of treatment of the animals they take care of. Ivermectin is one of the antiparasitic remedies with numerous advantages. It is a broad-spectrum drug, effective against both arthropod and nemathelminthic endo- and ectoparasites; it can be administered either orally or parenterally; it is potent – allowing for administration of very small doses, and its potency is far exceeding those of other anthelmintics (Fink, 1988; Soll, 1989). These attributes have led to the extensive use of the compound for treating parasitic infections in a variety of animals. However, its possible toxicity should be taken into consideration. The main concern is neurotoxicity, which in most mammalian species may manifest as central nervous system depression, and consequent ataxia. Most often this happens when the drug has been overdosed and may cross the blood–brain barrier. Clinical evidence suggests kittens are susceptible to ivermectin toxicity (Frischke & Hunt, 1991), and for some breeds of dogs the drug is contra-indicated. There are data that ivermectin can cross the blood–brain barrier in tortoises, often with fatal consequences. Apart from domestic animals, ivermectin has been approved by various regulatory authorities for use in camels and Reindeer only. The treatment of any other species with the product is considered to be “extralabel” usage (Soll, 1989).

It is obvious that together with the conveniences, the administration of ivermectin in wild animals has its specificities and holds a great amount of risks. The purpose of the present work was chosen in that respect aiming at the completion of a literature review of the experience in the treatment of wild animals with ivermectin, encompassing in our case only the studies on the treatment of helminthoses in the ones held in captivity. We hope that the obtained data would be of use both to the researchers in the field of parasitology and the practicing specialists in the zoos, wild animal hospitals, rescue-shelters, rehabilitation centers, reserves and others.

Materials and Methods

The results found in the literature are presented in a chronological order and are grouped according to the taxonomic classification of the animals.

Results

Use of Ivermectin in Mammals

Ivermectin has been introduced in 1981 (Campbell, Burg, Fisher, & Dybas, 1984). Shortly after, Frolka and Roštínská (1985) have used it to treat various animals at the Gottwaldov-Lešná Zoo in Czechoslovakia. The drug has been applied as Ivomec subcutaneous (s.c.) or Eqvalan intramuscular (i.m.) 200 µg/kg body weight (b.w.), respectively 1 ml/50 kg and 1 ml/100 kg (b.w.). Ivomec has cured infections with gastrointestinal nematodes (*Nematodirus*, *Trichuris*, *Trichostrongylus*, *Ostertagia*, *Cooperia*, *Haemonchus*, *Chabertia*) in eight antelopes but has been ineffective against *Eimeria*. Nematode ova of four of the genera have reappeared in the feces after six months and a second dose of 0.7–1.0 ml/animal has given full cure. Ivomec has been ineffective against heavy *Trichuris* infection in a five-year-old Bactrian camel. Following Eqvalan treatment of three Shetland ponies with large strongyles and one with *Parascaris equorum*, all have been free of infection at fortnightly fecal examinations for three months. Both formulations have been without side effects (except for swelling and increased sensitivity at the injection site) even in animals who have received doses above the recommended dose and in pregnant ones.

Meningeal worm *Parelaphostrongylus tenuis* has been occurred in six *Rangifer tarandus tarandus*, two *Hippotragus niger* and one *Oryx dammah* at the National Zoological Park's Conservation and Research Centre, USA (Nichols, Montali, Bush, Phillips, & Collins, 1986). Clinical signs have begun with ataxia of the rear legs, often progressing to paraplegia. The front legs have been affected to a lesser degree. Treatment of three *R. tarandus* with dexamethasone at 1 mg/kg intravenous (i.v.) and levamisole at 5.5–11.0 mg/kg s.c. and of one *H. niger* with dexamethasone and ivermectin at 0.6 mg/kg i.m. has given initial mild improvement, but eventually all animals either have died or have been euthanized through complicating of the disease.

An apparently healthy Cynomolgus monkey (*Macaca fascicularis*) has died two hours after routine inhalation anesthesia and implantation of a femoral catheter (Kornegay, Giddens, Morton, & Knitter, 1986). Gross necropsy findings have included patchy raised areas of severe pulmonary hemorrhage and consolidation. Filarioid nematodes (*Edesonfilaria malayensis*) have been located in pulmonary blood vessels and in numerous 0.1–2 cm fibrous cysts on the pleural surfaces of the lungs, pericardium, diaphragm, retroperitoneum, and in the urinary bladder wall. Microscopic lesions have included verminous vasculitis, pulmonary infarcts and pneumonia. Many of the nematodes have been more necrotic than the surrounding host tissue. During quarantine, 17 days before surgery, the monkey has been given a single dose of ivermectin (200 µg/kg, i.m.) as an anthelmintic for gastrointestinal nematodes. The authors postulate that many of the filarioid nematodes have been killed by this treatment. These parasitic emboli have caused pulmonary infarction and the severe inflammatory reaction. The resulting pulmonary disease has compromised pulmonary function and contributed to death after anesthesia. This complication should be considered if monkeys possibly harboring filarioid nematodes are treated with ivermectin.

Ivermectin 200 µg/kg b.w. has been given by s.c. injection to hedgehogs (*Erinaceus europaeus*) in the Sofia Zoo, Bulgaria (Matevsky & Mutafova, 1987). The treatment has been 100% effective against lungworm infection with *Crenosoma lophocara* but *Capillaria*

exigua has not been controlled even by a second treatment with ivermectin 400 µg/kg given two months later.

Mak, Lam, Noor Rain, and Suresh (1988) have recorded that ivermectin single doses of 0.2–1.0 mg/kg b.w. have reduced the microfilarial counts of subperiodic lymphatic filariid nematode *Brugia malayi* in monkeys *Presbytis cristata* by 59.9–89.6% of initial counts, four weeks after treatment. Adult filaricidal activity has been poor, and live adult worms have been recovered from all animals at autopsy. There have been no serious side effects at these doses.

Kreeger, Seal, Callahan, and Beckel (1990) have described their try with anthelmintic treatment of captive Gray wolves (*Canis lupus*). Thirteen of 24 animals have been infected with the heartworm, *Dirofilaria immitis*. Wolves have been treated with 2.2 mg/kg sodium thiacetarsamide i.v. b.i.d. for two days to eliminate adult heartworms, given 5.0 mg/kg acetylsalicylic acid orally for two weeks to reduce myointimal proliferation and thromboemboli, and given 0.2 mg/kg ivermectin s.c. four weeks after beginning therapy to eliminate microfilariae. All animals have survived the treatment. Four wolves have developed coughing episodes after adulticide administration. Thiacetarsamide has not eliminated adult *D. immitis* in one wolf, but ivermectin has been completely effective in eliminating microfilariae. Seven of eleven adult wolves without heartworm and three pups have been infected with *Ancylostoma caninum* and/or *Toxocara canis*. All animals, whether infected or not, have been treated with 0.2 mg/kg ivermectin given s.c. Blood samples have been taken from adult wolves for hematologic analyses before and 35 days after treatment. No ova have been detected upon fecal reexamination 35 days post treatment. Prior to treatment, wolves with ancylostomiasis have had hypochromic anemia when compared with non-infected animals. After treatment for either heartworm or hookworm, twelve of 24 wolves have been given 0.05 mg/kg ivermectin once monthly for the next 18 months. The other twelve wolves have been untreated for the same period of time to serve as control animals. At the end of this period, no treated wolf has had heartworm. No ova have been found in any of the treated wolves, whereas seven of twelve control animals have been positive for *A. caninum* and one of twelve animals has been positive for *T. canis*. Finally, the authors have summarized that in these wolves, ivermectin has been effective in the elimination of *D. immitis* microfilariae, *A. caninum*, and *T. canis*, without any adverse tissue reactions, and has been effective for prophylaxis of heartworm and hookworm administered at 0.05 mg/kg monthly.

Isaza, Courtney, and Kollias (1990) have documented, through a mailed questionnaire survey, the methods of parasite control currently used in captive wild ruminants. The majority of respondents have indicated that they use parasite surveillance and identification technique similar to those used for domestic ruminants. Of the four major anthelmintic drug classes, the benzimidazoles and ivermectin have been used most commonly. Many of the parasite control programs have had high treatment frequencies which have been similar to dosing frequencies reported to result in anthelmintic resistance in domestic animals. Lack of effectiveness by benzimidazoles has been perceived to be a problem by many respondents.

The anthelmintic effectiveness of various dosages of ivermectin administered i.m. has been compared in three groups of Raccoons (*Procyon lotor*) infected with nematode parasites (Hill, Zimmerman, Greve, & Beran, 1991). Qualitative fecal examinations have been performed before treatment and periodically after treatment using a sucrose flotation technique. Ivermectin has been effective against *Placoconus lotoris*, *Capillaria putorii*, and

Physaloptera sp. at all doses (200–2000 µg/kg b.w.) and against *C. plica* at higher doses (> 600 µg/kg b.w.). Ivermectin has been incompletely effective against *Baylisascaris procyonis* and *C. procyonis* at a dose of 2000 µg/kg b.w.

The efficacy of six anthelmintics against natural infections of *Baylisascaris procyonis* in Raccoons ($n = 7$ per drug) has been determined by [Bauer and Gey \(1995\)](#). The tested compounds have been the following: pyrantel embonate as a 43.9% paste formulation for horses, ivermectin as a 1% injectable formulation, moxidectin as a 0.1% drench formulation for sheep, albendazole as a 10% drench formulation for cattle, fenbendazole as a 18.75% paste formulation for horses and flubendazole as a 4.4% gel formulation for dogs and cats. Pyrantel embonate (20 mg base/kg b.t.), ivermectin (1 mg/kg b.w.) and moxidectin (1 mg/kg b.w.) have been given once; albendazole (50 mg/kg b.w./day), fenbendazole (50 mg/kg b.w./day) and flubendazole (22 mg/kg b.w./day) have been administered once daily for three consecutive days. The doses of the liquid and paste formulations have been measured using a calibrated syringe or weighed, respectively, to ensure accurate dosage, then mixed with small amounts of moist cat food and fed to the Raccoons. The efficacy of each anthelmintic compound has been estimated in terms of series of critical tests. Furthermore, post mortem examinations seven days after the end of treatment have been performed and no roundworms have been detected in any Raccoon. On the basis of their results the authors suggest that any of the six anthelmintics can be used at the dose rates tested in a deworming program for captive Raccoons.

Mebendazole and ivermectin have been studied for the control of gastrointestinal helminthiasis in three species of captive gazelles: *Gazella dama mhorrr*, *G. cuvieri*, and *G. dorcas* ([Abaigar et al., 1995](#)). Ivermectin has been given s.c. in a single 0.2 mg/kg live-weight dose and mebendazole has been given in three dosages based on species: *G. dorcas*, 14 mg/kg; *G. cuvieri*, 6 mg/kg; and *G. dama*, 3 mg/kg orally twice daily for three consecutive days. Each drug has been tested in 13 individuals of each species; 13 additional individuals have served as untreated controls. Helminths detected by fecal examination and culture have been species of *Trichuris*, *Ostertagia*, *Cooperia*, *Trichostrongylus*, *Nematodirus*, and *Strongyloides*. The prevalence among the total gazelle population has been *Trichuris* 55%; *Nematodirus* 26%; and other nematodes 84%. After treatment with mebendazole, the nematode egg counts and the number of animals shedding eggs have decreased moderately. After ivermectin treatments, there have been marked decreases in the amount of eggs being shed and the number of animals shedding eggs of these nematodes.

[Conboy and Adams \(1995\)](#) have described a case of male and female Silver foxes (*Vulpes vulpes*) diagnosed with naturally acquired infections with lungworm *Crenosoma vulpis* at the Cherry Brook Zoo in St. John, New Brunswick, Canada. The main clinical sign has been a chronic cough. Crenosomiasis has been diagnosed by fecal examination using the Baermann technique. The foxes have been treated with a s.c. injection of ivermectin (200 µg/kg). Clinical signs have been resolved, and fecal exams have been negative at three and six week post treatment. No adverse reactions to the drug have been observed. The authors have noted that due to the small number of animals involved and the absence of post treatment necropsy/worm recovery data, this indication of efficacy must be viewed as circumstantial until further testing.

Seventeen wild-caught white-faced Capuchin monkeys (*Cebus capucinus*) have been diagnosed with infections of the metastrongylid lungworm *Filariopsis arator* Chandler,

1931 (Lee, Boyce, & Orr, 1996). Treatments with ivermectin, fenbendazole, thiabendazole, mebendazole, and pyrantel pamoate have not been effective in controlling these parasites. However, administration of albendazole at 15 mg/kg p.o. (b.i.d.) for 14 days has eliminated the shedding of nematode larvae in the feces and killed adult worms in the lungs.

Toxascaris leonina eggs have been detected in the feces of nine out of 28 carnivores (Families: Felidae, Canidae and Viverridae) kept at Khartoum Zoo, Sudan (Sayid & Mohammed, 1997–1998). Infected animals have shown signs of diarrhea alternated with constipation, rough coat and sometimes focal or generalized alopecia. Adult worms have been detected in the feces of infected animals, while the larvae – in the water troughs in the cages where animals have been kept. Treatment with thiabendazole alone has not been effective in all infected animals. Treatment with piperazine has resulted in total clearance of infection in jackal and mongoose, but has not been effective in lions and leopards. The use of ivermectin (“Oramec-drench”, MSD, Agvet-Holland at 2.5 ml/kg b.w.) when persistent infection has been detected in addition to direct flaming of the floor and troughs has resulted in effective treatment and control of the infection.

According to Lamka, Ducháček, Nevole, Hejralová, and Šesták (1997), the qualitative and quantitative parasitological differences between domestic and wild sheep (mouflon) exist. That is why these authors have performed a study aiming to describe anthelmintic efficacy of ivermectin administered in different doses and to select the optimum dose. It has been realized during winter season in game herd in 23 ten to eleven months old mouflons. Before treatment larvae of *Muellerius capillaris* (strong infection) and eggs of *Nematodirus* spp. and *Oesophagostomum* spp. (mild infection) in common fecal samples have been found. The mouflons have been randomly divided in four groups (control group and three experimental groups). Before experimental treatment each animal in experimental groups has been weighed and marked. The doses of ivermectin 0.20, 0.60, and 1.00 mg/kg of b.w. have been used. The drug has been administered s.c. All mouflons have been placed into an enclosure of four hectare. 28–60 days after treatment mouflons have been hunted and detail helminthological examinations (lung macroscopical evaluation, larvoscopy of lung verminous spots, larvoscopy and oviscopy of individual feces, necropsy of gastrointestinal organs and quantification of nematode adults) have been carried out. Larvae per gram (LPG) and eggs per gram (EPG) values have been determined. The study has been realized as a simple blind experiment – all helminthological examinations have been done without knowledge of the used therapy or ivermectin dose. Macroscopical examinations of lungs have showed symptoms of strong *M. capillaris* infection (numerous verminous spots) in all 23 mouflons. Larvoscopical examinations (lung tissue, individual feces) after treatment have become negative in 19 treated animals. In the rest of animals the mild larvoscopical finding has been determined. Pretreatment common LPG values in control animals have been confirmed, findings in verminous spots of these animals have been highly positive (massive presence of live larvae, eggs, and rests of nematode adults). In respect to reached results, pathogenity of found nematodes, age of experimental mouflons, and economy of treatment, a dose of 0.60 mg/kg b.w. ivermectin as optimum for parenteral treatment of mouflon nematodoses has been recommended.

During the study of helminthological status of leopards from the Nehru Zoological Park, Hyderabad, ancylostomid infection has been established (Suresh, Choudhuri, Kumari, Hafeez, & Hamza, 2000). The animals also have exhibited clinical symptoms of the disease.

The affected leopards have been treated with ivermectin (200 µg/kg b.w.) given i.m. with the help of blow pipe. Clinical improvement along with parasite eggs per gram of feces have been monitored on days three and seven after therapy and thereafter at weekly intervals for one month. The results have proved that ivermectin has been safety and quite efficacious in this case as evident by a gradual but marked improvement in the clinical symptoms by the seventh day of initiation of treatment as well as fecal examination in which EPG have been 0 on the 7th day following therapy.

Ortiz et al. (2001) have compared seven different methods of administering ivermectin to gazelles: subcutaneous injection, direct oral administration, administration in individual feeds, administration in a herd feed, direct oral administration of a second ivermectin formulation, administration in individual water supplies, and administration in the herd's water supply. The first five treatments have been effective, as monitored by fecal egg count reduction tests, and administration in individual feeds or in a herd feed have avoided the need to capture the animals, with the attendant risk of mortality. Of the factors associated with the recipients (species, sex, age and inbreeding coefficient) age has been the only significant factor for the efficacy of the treatment. Oral or subcutaneous, individual or collective, and direct or indirect administrations have been equally satisfactory for the treatment of all the parasite groups studied. Only when parasitic problems have been due to *Nematodirus* species direct administration to individual animals appear to be preferable.

Forty Dog-faced fruit bats (*Cynopterus brachyotis*) have been administered one drop of 1% ivermectin topically as a part of routine physical exam and deworming program, and eleven have developed sudden generalized paresis (DeMarco, Heard, Fleming, Lock, & Scase, 2002). Six of the bats have been recovered within 24–48 hours, and the remaining five have been presented recumbent and weak to the University of Florida Veterinary Medical Teaching Hospital. Ivermectin toxicosis has been suspected, and the admitted bats have died or have been euthanatized within three to five days of the development of clinical signs despite supportive care. Three of the dead bats have had renal tubular. Burkholder, Jensen, Chen, Junkins, Chatfield, and Boothe (2004) have studied plasma levels of the parasiticide ivermectin by high-performance liquid chromatography in five Llamas (*Lama glama*) after single 200 µg/kg s.c. injections. Ivermectin levels have been undetectable in plasma samples drawn up to four weeks after injection, suggesting that the dosage used has been insufficient to reach therapeutic concentrations in this species.

Singh et al. (2006) have investigated the prevalence and chemotherapy of parasitic diseases in carnivores at Mahendra Choudhury Zoological Park, Chhatbir, Punjab. Two panthers, having *Ancylostoma* spp. infection, have been treated with ivermectin – 200 µg/kg b.w. i.m. using a dart gun. The reduction in fecal egg count has been 63.4% on day two post treatment. The reduction has been 100% on day five post treatment. Thus ivermectin 200 µg/kg b.w. has been found to be 100% effective in control of *Ancylostoma* spp. infection in panthers and seem to be the good drugs of choice to control worm burdens.

Goossens, Vercruysse, Vercammen, and Dorny (2006) have evaluated three parasite control programs in seven herds of captive wild ruminants in three consecutive years. In the first year, a biannual spring–summer treatment regime with fenbendazole at 7.5 mg/kg b.w. per os (p.o.) for three days has been applied. The next year, an early-season treatment program with three administrations of fenbendazole at the same dosage at three-week intervals has been used. In the third year, an early-season treatment program with ivermectin (0.2 mg/kg

p.o. for three days), applied three times at five-week intervals, has been evaluated. Effectiveness of these control programs has been assessed by fecal egg counts and by scores of body condition and fecal consistency at weekly intervals. Involved animal species have been Arabian oryx (*Oryx leucoryx*), Scimitar-horned oryx (*Oryx dammah*), Slender-horned gazelle (*Gazella leptoceros*), Soay sheep (*Ovis aries soay*), Ibex (*Capra ibex*), Red deer (*Cervus elaphus hippelaphus*), and Nelson's elk (*Cervus elaphus nelsoni*). With the spring–summer regime, fecal egg counts have remained low during the first five months, but from September onward, they slowly have increased to significant levels in all seven herds. The early-season program with fenbendazole has resulted in fecal egg counts near zero during the entire year in four herds but a significant egg shedding from August onward has been noted in Arabian oryx, Scimitar-horned oryx, and Soay sheep. The early-season program with ivermectin has resulted in very low to zero egg shedding in gazelle, adult Soay sheep, Ibex, Red deer, and Nelson's elk during the entire grazing season, but has failed to prevent high shedding in October in Arabian oryx and Scimitar-horned oryx. According to the authors failure of the treatment regimes in some herds may be explained by high contamination of grassy pastures with infective larvae/eggs in the previous year or before the first treatment.

The efficacy of two broad spectrum anthelmintics (ivermectin and levamisole) against the nematode *Nematodirus spathiger* in the Reem (Arabian sand gazelle) and Idmi (Arabian mountain gazelle) at King Khalid Wildlife Research Centre has been determined by Mohammed, Omer, and Sandouka (2007). Gazelles of both species naturally infected with *N. spathiger* have been each divided into three groups. Groups one and two (six gazelles each) have received subcutaneous doses of ivermectin (200 mg/kg b.w.) and levamisole (7.5 mg/kg b.w.), respectively. The last group has been left as untreated control. Fecal egg counts have been employed to determine the efficacy of the two drugs against *N. spathiger* infection in both gazelle species. Reduction in arithmetic mean fecal egg counts achieved by ivermectin and levamisole in the Reem gazelles has been 94% and 89.3%, respectively. The reduction in the Idmi gazelles has been 97.2% and 96.4%, respectively. Both anthelmintics have appeared to be more effective in the Idmi gazelles than in the Reem gazelles, however, there has been no significant difference in the fecal egg reduction tests in both animal species.

Numerous cases of *Congylonema* spp. infection with associated pathological lesions and clinical signs have been identified in a collection of Goeldi's monkeys (*Callimico goeldii*) (GMs) at a zoological park during a three-year period (Adkesson, Langan, & Paul, 2007). An increase in the incidence of clinical signs in the GMs and other callitrichid species has prompted an investigation to determine the prevalence of infection within the collection and evaluate treatment protocols. Twenty-one callitrichids [nine GMs, four Golden lion tamarins (*Leontopithecus rosalia*), six Cotton-top tamarins (*Saguinus oedipus*), and two Golden-headed lion tamarins (*Leontopithecus chrysomelas*)] have been included in this study. Many of the animals have been positively diagnosed on past examinations. Repeated cytological evaluations of scrapings taken from the mucosa of the tongue have been performed to diagnose infection. The animals have been randomly divided into two groups and treated with either ivermectin (290 µg/kg p.o., once a week for four consecutive weeks) or mebendazole (70 mg/kg p.o., once a day for three consecutive days). Follow-up scrapings have been performed on all animals at days 35, 64, and 156. Numerous animals have displayed clinical signs (facial pruritis, inflammation, and ptialism) before and throughout the

investigation; however, *Gongylonema* spp. infections have been only confirmed by tongue scrapings in two animals. Fecal floatation for recovery of spirurid eggs also has been performed, but it yielded no positive results. The low number of confirmed cases has precluded comparative evaluation of the efficacy of the anthelmintic treatment protocols. However, according to the authors both regimes have seemed subjectively similar in decreasing clinical signs and have been safe with no adverse effects. They also say that diagnosis of *Gongylonema* spp. infection is challenging, even when severe clinical signs are present. Their investigation further has demonstrated the lack of a reliable ante-mortem test for the parasite and underscored the importance of treatment based on clinical signs.

Loxodonta africana are susceptible to a wide variety of parasites that are often treated with the broad spectrum antiparasitic ivermectin based on empirical knowledge. In connection with that [Gandolf et al. \(2009\)](#) have performed some studies. Their goals have been the followings: (1) measure plasma ivermectin levels after administration of 0.1 mg/kg p.o., (2) compare plasma ivermectin levels following administration with regular versus restricted feed rations, (3) measure ivermectin excretion in feces, and (4) use these findings to generate dosing recommendations for this species. Based on their results, the authors express an opinion that administration of 0.2–0.4 mg/kg ivermectin p.o. should be appropriate for eliminating many types of parasites in elephants, and could minimize development of parasite resistance.

In another study concrete schemes of ivermectin application in elephants and results of the treatment are presented ([Oo, Mar Kyaw, Nyunt, & Khaing, 2009](#)). The authors have tested sixty elephants for microfilaria. From those found to be infected with microfilaria, ten have been selected randomly and divided into two groups: I1 and I2. Five elephants have been randomly selected from the elephants not detected as being infected with microfilaria, which have formed a control group – C. Group I1 has been treated with ivermectin at day 0 and group I2 has been treated at day 0 and day 15. The group C has not been treated. Ivermectin 10 mg/ml has been administered subcutaneously to elephants naturally infected with microfilaria in a dosage of 1 ml/100 kg b.w. Blood samples have been collected from the 15 animals on days 0, 15, 30, 60, 90 and 120 to determine microfilaria titers and to assess blood parameters. Fecal egg counts of all 15 elephants have been done at days 0, 15, 30, 60, 90 and 120. The dosage of ivermectin has been half of the usually recommended one. The results of this study have showed that all microfilariae have been cleared off in the peripheral blood of experimental animals after treatment at day 15. Thereafter, microfilariae infestation has not been observed in the treated groups until day 90. On day 120, both treated groups have been re-infected with microfilaria. Mean values of eggs per gram significantly have decreased after injection of ivermectin in the treated groups. The authors have concluded that a single dose of ivermectin (1%) administered s.c., not only reduces the density of microfilariae in elephant's peripheral blood but also significantly decreases gastrointestinal nematodes. A single dose of ivermectin (1%) in half recommended dose is effective for the clearance of microfilaria for up to three months. Therefore, the drug should be administered four times per year to elephants.

The efficacy of medicated food pellets (containing 10 mg of ivermectin per kg) has been evaluated for the control of intestinal strongyles in a group of captive zebras (*Equus burchelli*) ([Lia et al., 2010](#)). The egg reappearance period and the fecal egg counts in terms of eggs per gram of feces have been investigated. From day 0 until day +9, 30 zebras have

been fed with medicated pellets and pooled fecal samples have been collected from the floor of paddocks. The drug has shown an efficacy of 100% for up to 78 days post-treatment, with one exception. The authors have concluded that the administration of ivermectin with medicated food pellets is effective in controlling intestinal strongylosis in captive zebras. The opportunity to treat captive ungulates with an in-feed anthelmintic has been discussed in relation to the fractious nature of these animals, which often impairs helminth control programs in zoo-parks.

Lan et al. (2012) have described their experience in applying of ivermectin in Red pandas (*Ailurus fulgens*). Ten of the 48 animals in the Chengdu Research Base of Giant Panda Breeding, Sichuan province, China, have died after prolonged periods of depression, weight loss, and mucocutaneous membrane xanthochromia. During postmortem examination, live heartworms have been found in the right cardiac ventricles and pulmonary arteries of all ten animals. Selamectin and ivermectin have been used for clinical prophylaxis in the remaining Red pandas. The authors have observed a gradual decrease in morbidity and mortality during this period. After that all Red pandas have received ivermectin prophylactic treatment at monthly intervals instead of selamectin, because ivermectin has been more convenient for long-term prophylaxis without a necessity to anesthetize the animals before its oral administration. However, regular fecal examinations for eggs of intestinal worms have indicated that the pandas have been infected by *Baylisascaris ailuri* roundworms. The dose of ivermectin which has been used as a preventive drug against heartworms has been 6 µg/kg. In this case, the dosage at 200 µg/kg has been used not only to prevent heartworms, but also to prevent *B. ailuri*. After administration of the drugs, no side effects have been observed in any of the pandas. Although both selamectin and ivermectin are considered to be safe for gravid dogs and cats, these drugs have not been used for prophylaxis on these rare animals during conception and lactation at the beginning as a precautionary measure. No case of dirofilariosis has been observed in that year. However, four cases have appeared in newborn pandas next year. Therefore, heartworm chemoprophylaxis has been performed on all Red pandas, including young ones. No *D. immitis* infection cases have been observed after that. Finally, the authors have concluded that selamectin and ivermectin have been successfully used to control and prevent heartworm disease in Red pandas. As a precautionary measure, they have also advised of decreasing the preventive dose of ivermectin against heartworms to 50 µg/kg, which is known to be well tolerated even by gravid or young animals. Young pandas should be treated as soon as possible after birth and then continually with a monthly administration of heartworm prophylaxis.

During the study on helminths in captive Cheetahs in Namibia two wild five-year-old (estimated age) male cheetahs, whose home range includes the Cheetah Conservation Fund (CCF) facilities, have been anesthetized and investigated for parasites (Meny, Schmidt-Kuntzel, & Marker, 2012). Although deworming of wild Cheetahs has not been normal practice at CCF, the high parasite load (*Ancylostoma* sp.) and possibility to include the two males in this parasitology study have led to the decision to deworm the two Cheetahs with a single injection of ivermectin (10 mg, Ivomect, Merial Inc., Duluth, Georgia 30096, USA). Eleven days later, two fresh scat samples have been found near the captive cheetah enclosures after the two males had been sighted at the CCF research center. One sample has been assigned genetically to one of the two wild Cheetah males and it has been negative for the presence of parasite eggs.

We did not establish any results about using of ivermectin in captive Macropodidae. On the other hand, they are common inhabitants in the zoos. That is why we decided to include the next study in the review. Cripps, Beveridge, and Coulson (2013) have conducted three field experiments on free-ranging Eastern grey kangaroos (*Macropus giganteus*) at a golf course in Victoria, Australia, treating animals with the anthelmintic drugs moxidectin (s.c., 1 mg/kg, 2 mg/kg), ivermectin (s.c., 200 µg/kg), and albendazole (p.o., 3.8 mg/kg). After treatment they have monitored strongylid fecal egg counts (FECs) over time and assessed anthelmintic efficacy using fecal egg count reduction tests (FECRTs). They have also performed a larval development assay (LDA) to evaluate directly the efficacy in the nematode population. Unexpectedly, moxidectin and ivermectin have had low efficacy with maximum FEC reductions of 2% and 28%, respectively. However, treatment with albendazole has reduced FECs by 100% in all kangaroos and egg counts have remained low for up to three month. The results from the LDA have supported the FECRTs, with low macrocyclic lactone efficacy and high albendazole efficacy. Macrocyclic lactones, at recommended dose rates, have been much less effective against strongylid nematodes in kangaroos than has been reported for domestic herbivores. According to the authors this may be partly due to pharmacokinetics in the host and partly due to low susceptibility in some of the nematodes infecting Eastern grey kangaroos.

Dehuri, Panda, Mohanty, and Sahoo (2013) have tested anthelmintic effectiveness of three drugs in lions from Nandankanan Zoo. Twenty-four animals have been studied for prevalence of nematode eggs by fecal sample analysis and the prevalence rate has been found to be 70%. For evaluation of anthelmintics, 20 lions have been considered and divided into four groups according to the drug administered and each group has been consisted of five animals. The lions have been administered pyrantel pamoate at the rate of 20 mg/kg b.w., levamisole at the rate of 4.4 mg/kg b.w. and ivermectin at the rate of 0.3 mg/kg b.w. Evaluation of anthelmintic activity against nematodes of lions has revealed that ivermectin at a dose rate of 0.3 mg/kg b.w. has reduced the fecal egg count of *T. leonina* and *Ancylostoma* spp. to 100% on 3rd day post treatment while in others it has been lesser. The reappearance of *T. leonina* infection in lions has occurred 24, 45 and 52 days of post treatment while the reappearance of *Ancylostoma* infection in lions has occurred 24, 31 and 45 days of post treatment in groups that have been administered with pyrantel pamoate, levamisole and ivermectin respectively. On the basis of their results authors have concluded that ivermectin at a dose rate of 0.3 mg/kg b.w. p.o. may be recommended for the treatment of *T. leonina* and *Ancylostoma* spp. infection in lions.

Nine ponies, 20 months of age, with cyathostome and pinworm infections have been treated orally with ivermectin at a dosage of 400 µg/kg (Scháňková et al., 2013). Ivermectin has been highly effective on the cyathostome infection. However, adult *Oxyuris equi* have been presented in six horses after treatment. The authors comment that in recent years, anthelmintic treatment with macrocyclic lactones has not appeared to deliver the expected efficacy against Equine pinworms (*O. equi*) in the USA. This has been the first European study which has demonstrated anthelmintic resistance in *O. equi* to macrocyclic lactones in ponies (Czech Republic).

A review of the literature on the experience accumulated in the antiparasite treatment of the ruminant animals of the Cervidae family has been presented by Panayotova-Pencheva, Salkova, and Trifonova (2015). The summed-up literature data have shown which of the

drugs have a good effect against the gastrointestinal and lung nematodes, extrapulmonary protostrongylids, trematods, cestods and external parasites. Ivermectin has been most efficient in the struggle both against the gastrointestinal and lung nematodes. Its efficacy in the fight against the pulmonary helminthoses has been better when applied at higher doses such as 400 µg/kg b.w. and in its s.c. and pour on administration as compared to p.o. one. The attempts for controlling the extrapulmonary protostrongylidoses with ivermectin has been the best of the rest of anthelmintics but also at the high dosage (400 µg/kg b.w.) though even in these cases its effect has been incomplete. In connection with the problem, here we would like to mention the study by Kocan (1985) who has indicated that ivermectin in a dose 100 µg/kg does not has a practical application for the elimination or prevention of *P. tenuis* infestations in White-tailed deer (*Odocoileus virginianus*). According to the author, however, routine use of this product may prove advantageous in temporary reducing the number of larvae shed in the feces of infected deer, thus minimizing environmental contamination with first stage larvae.

Use of Ivermectin in Birds

Kock, Henderson, Appleby, Hawkey, and Cinderey (1987) have reported for an outbreak of *Echinuria uncinata* infection causing deaths in *Branta ruficollis* and *Cygnus melanocoryphus* at the Whipsnade Zoo, UK. Some of the birds have been imported from other wildfowl collections in the UK two years ago. Attempts to confirm infection by fecal tests have failed. The authors have described clinical, hematological and pathological changes in the birds. It is reported that s.c. injections of ivermectin 200 µg/kg b.w. in conjunction with antibiotics substantially have improved the condition of the animals.

Avian haematozoa and microfilaria have been found in the blood of two recently imported, adult Salmon-crested cockatoos (*Cacatua moluccensis*) and an adult Lesser sulphur-crested cockatoo (*C. sulphurea*) at Kove Oji Zoo (Murata, 1990). Gametocytes observed in the blood cells of *C. moluccensis* have been banana-shaped or amoeboid and extended along the host cell nucleus. A few schizonts and numerous trophozoites have been also found. The gametocytes in *C. sulphurea* have extended around the host cell nucleus. The cytoplasm of this organism has stained pale blue and has contained pigment granules which have been randomly distributed. The former haematozoon has been identified as a *Plasmodium* sp. and the latter as a *Haemoproteus* sp., probably *H. handai* on the basis of its morphology. The microfilariae have had rounded anterior ends with straight tails and many dark purple stained nuclei. Two i.m. injections of ivermectin 1450 µg/kg have been effective in treating the microfilarial infections. A compound, consisting of pyrimethamine and sulfadoxine, has been given orally for three days at a dosage of 12 mg/kg/day and 245 mg/kg/day, respectively, but the effect of these compounds on the *Plasmodium* infection has not been determined.

Suedmeyer, Bermudez, and Kazacos (1996) have described a case of some Emus (*Dromaius novaehollandiae*) parasitized by *Baylisascaris* sp. One of them (three-month-old female) has died with signs of cerebellar nematodiasis. Despite the treatment with ivermectin another Emu has exhibited cerebellar signs identical to those of died bird. Two additional Emus have been clinically normal. The three Emus have been first treated prophylactically once weekly with ivermectin (200 µg/kg p.o.) and then have been given daily

pyrantel tartrate pellets. The authors consider that although treatment of clinical cases of *Baylisascaris* infection with ivermectin has had equivocal results, weekly prophylactic treatment with ivermectin 200 µg/kg p.o. may prevent neurogenic migration of this parasite.

An adult, wild-caught, female Prairie falcon (*Falco mexicanus*) has been presented with the chief complaint of anorexia (Hawkins, Couto, Tell, Joseph, & Lowenstine, 2001). Radiographic findings have included increased densities within the air sacs, and coelomic endoscopy revealed numerous slender worms within the air sacs and on the serosal surfaces of the ovary, oviduct, liver, proventriculus, and ventriculus. Ivermectin 200 µg/kg p.o. and dexamethasone sodium phosphate have been administered as single treatments. Prophylactic antifungal and antibiotic therapies with fluconazole and amoxicillin with clavulanic acid have been instituted. Nutritional and caloric support has been provided by force feeding thawed, frozen mice. Three days after the ivermectin treatment, fenbendazole 25 mg/kg p.o. s.i.d. has been administered for three days. The condition of bird has been improved for a short period of time with that therapy. Twenty-one days after initial presentation, the bird has become recumbent with increasing pelvic limb neurologic deficits and has been euthanized. On histopathologic examination, mature nematodes and larvated eggs identified as *Serratospiculoides amaculata* have been found within the subdural space of the distal thoracolumbar and synsacral spinal cord and within the coelomic cavity. Authors suggest that *S. amaculata* can cause clinically significant lesions in its falconiform host with potentially fatal results.

Samour and Naldo (2001) have also pointed that serratospiculiasis is a danger disease in falcons. In that review article they have noted that treatment of the disease with ivermectin has been routinely at the dosage of 1 mg/kg s.c. repeated one or two weeks later without observing any detrimental effects.

Naturally occurring *Serratospiculum seurati* infestation has been diagnosed in 149 (8.7%) out of 1706 captive falcons (Tarello, 2006). Infestation has been symptomatic in 107 (71.8%) and non-symptomatic in 42 (28.2%) birds. Clinical signs more often have been dyspnea (58.8%), reduced speed and strength in flight (56%), weight loss (38.3%), anorexia/poor appetite (22.4%) and lethargy (16.8%). 140 of the animals have been treated with melarsomine at dosage of 0.25 mg/kg injected i.m. for two days, and ivermectin, injected once at the dose of 1 mg/kg, ten days later. After administration of melarsomine, signs have disappeared within one to ten days in symptomatic birds and improvement of flight performances has been noted in non-symptomatic birds. Dead adult parasites have been ejected in 22 cases. Embryonated eggs have not been detected in coproscopic checks made ten and 40 days after the end of therapy, in association with lasting clinical remission. According to the author, the main conclusion of this work is that *S. seurati* is overall pathogenic for birds of prey in the Middle East and that melarsomine and ivermectin can be an effective protocol of therapy eliminating both clinical signs and parasites.

In another study, the same author (Tarello, 2008) has reported the following results: 52 captive falcons out of 3988 (1.3%) raptors microscopically examined for intestinal parasites in the Middle East have been proved infested with hairworms (capillariid parasites). Twenty-six of them (50%) have shown concurrent parasitoses. In the group of 26 falcons diagnosed with capillariosis as sole infestation (50%) compatible clinical signs such as anorexia, weight loss, weakness, dyspnea, regurgitation of food and blood, diarrhea and dark tarry feces, have been recorded. These birds have been treated intramuscularly with ivermectin

at doses of 2 mg/kg. In fecal samples examined 10–15 days later, the eggs of capillariid parasites have been disappeared, in association with complete clinical recovery.

Prevalence and chemotherapy of nematodes infestation and its effect on various blood parameters in pigeons have been studied by Basit, Pervez, Avais, and Rabbani (2006). One hundred wild and domestic pigeons have been subjected to coprological examination for the presence of nematode eggs. From these naturally infested pigeons, forty wild and forty domestic pigeons have been selected and divided into eight groups W1, W2, W3, D1, D2, D3, CW and CD each comprising ten pigeons. Pigeons of groups W1, W2, W3, D1, D2, and D3 have been treated with ivermectin 200 µg/kg b.w. s.c., oxfendazole 1 ml/3 kg b.w. p.o. and piperazine 2 g/l of drinking water, respectively. The pigeons of groups CW and CD have been kept as untreated control. The overall prevalence of nematodes infestation has been 57% whereas it has been 60% and 55% in wild and domestic pigeons, respectively. The efficacy of ivermectin, oxfendazole, and piperazine in domestic pigeons has been 100%, 60%, and 80% respectively, whereas it has been 100%, 50%, and 80% in wild pigeons, respectively.

Thelazia anolabiata is a spirurid nematode living in the orbits of birds which can cause lacrimation, keratitis, conjunctivitis, and corneal ulcers. This species has been reported from an Andean Cock of the Rock, *Rupicola peruviana* (Passeriformes: Cotingidae), from a zoo in Lima, Peru (Elias, Mamani, Hermoza, & Kinsella, 2008). Clinical signs of keratoconjunctivitis have been resolved with applying of ivermectin (0.2 mg/kg i.m.), ciprofloxacin, and an epithelium regenerator, and the host has been in good health after the treatment.

Ten wild Tawny frogmouths (*Podargus strigoides*) have been found in poor body condition on the ground and unable to fly and have been taken to Wildlife Hospital in Australia (Gelis, Spratt, & Raidal, 2011). Clinical examination has revealed paresis with variable but generally weakened deep pain responses, withdrawal reflexes and an inability to perch. Severely affected birds that failed to respond to anti-inflammatory, antibiotic and anthelmintic treatments all have had larval *Angiostrongylus cantonensis* in the brain and or spinal cord, with occasional larvae found in the visceral organs. Other parasites detected have included the liver fluke, *Brachylecithum podargi*, the intestinal nematode, *Allodapa suctoria*, an unidentified species of *Trichostrongylus* and unidentified cestodes. Gametocytes of *Leucocytozoon* sp. have been found in peripheral blood smears and low numbers of microfilariae have been found in histological sections of various blood vessels of several birds. However, no adult filarioids have been recovered. Unidentified subcutaneous mites have been identified in the connective tissue of the thoracic inlet. Attempts to treat two birds with ivermectin (200 µg/kg i.m. daily for five days) or oxfendazole-praziquantel have been unsuccessful.

Use of Ivermectin in Reptiles

Five Red-footed tortoises (*Geochelone carbonaria*) treated for intestinal nematode parasitism with a single i.m. injection of ivermectin (0.4 mg/kg) have been found in a state of extreme paresis or flaccid paralysis (Teare & Bush, 1983). One tortoise has recovered normal motor function over the next seven to ten days. The remaining tortoises have died within three days of receiving the ivermectin. Following this accident the authors have

performed some experiments aiming to investigate the safety of ivermectin in chelonians. Nine Red-footed tortoises, two Leopard tortoises (*Geochelone pardalis*), three Eastern box tortoises (*Terrapene carolina carolina*), and two red-eared turtles (*Chrysemys scripta*) have been used. Studies in the Red-footed tortoise have showed that some paresis will occur with dosages as low as 0.05 mg/kg. At least three other species of chelonians have been found to be susceptible to ivermectin toxicosis at similar dosages (0.1 mg/kg or less). The Leopard tortoise has appeared to be the most susceptible of the species tested, consistently developing mild paresis with a dosage of 0.025 mg/kg. Death has occurred with dosages as low as 0.3 mg/kg. A dosage of 0.05 mg/kg has been found to be safe in Red-footed tortoises, provided that treatment has not been repeated at intervals of less than seven days. Following the completion of that study, the remainder ($n=23$) of the red-footed tortoises at the National Zoo have been given ivermectin weekly for six weeks, at a dosage of 0.05 mg/kg. Pretreatment fecal examinations of this group have been repeatedly positive for nematode larvae (*Proatractis* sp.) and eggs (*Kalicephalus* sp.). A fecal sample obtained after two doses of ivermectin has been negative for eggs and larvae. However, a female Red-footed tortoise that has died six days after the last ivermectin dose (from causes unrelated to the ivermectin treatment) has had numerous adult nematodes (*Proatractis* sp.) in the caecum and colon. Thus, according to the authors, more studies must be completed on ivermectin in chelonians before recommendations can be made concerning the efficacy of ivermectin in chelonians. However, here we have to mention the experience of the same authors (Teare & Bush, 1983) which has shown that ivermectin at a dosage of 0.4 mg/kg has been safe in other reptiles – Corn snake (*Elapha guttata*) and Dumerils monitor (*Varanus dumerili*). Corn snakes also have tolerated dosages of 1.0 mg/kg without apparent adverse clinical signs.

Matevsky and Mutafova (1987) have tested effectiveness of ivermectin in some animals from the Sofia Zoo, Bulgaria. Ivermectin 200 µg/kg b.w. has been given by s.c. injection and has been 100% effective against *Kalicocephalus viperae* in snakes (*Elaphe quatuorlineata*). However, *Hexametra* sp. in the snakes and in tortoise *Testudo graeca* has not been controlled even by a second treatment with ivermectin 400 µg/kg given two months later.

Both male and female filariid nematode *Foleyella furcata* have been found in the subcutaneous tissue and abdominal cavity of an adult male wild-caught Senegalese chameleon (*Chamaeleo senegalensis*) (Széll, Sréter, & Varga, 2001). Prior to the chameleon's death, a migrating worm has been seen under the skin in the abdominal and thoracic region. Huge numbers of small, sheathed microfilariae have been detected in the blood smears. The chameleon has been treated with a single dose (0.2 mg/kg s.c.) of ivermectin. Serious adverse reactions (complete inertia) have been developed within 24 hours after injection and lasted for seven days, indicating either ivermectin toxicity or a systemic reaction involving the release of endotoxins from the microfilariae dying in the bloodstream as a result of parasiticide therapy. Therefore, the authors recommend avoiding ivermectin treatment of chameleons infected with *Foleyella*.

Another author (Bielli, 2007) has described a case of wild-caught chameleon, *Furcifer pardalis*, with signs of skin discoloration and mild ataxia, infected with the *F. furcata*. Monthly treatment with low doses of ivermectin (10 µg/kg) has been initiated and the patient treated has been monitored for four months. The microfilaremia has been markedly reduced after the first treatment and virtually disappeared after the second administration of the drug and the patient has been improved dramatically. The author shows that despite

these encouraging results it is impossible, to date, to claim an adulticidal effect of this therapeutic plan. Caution should be paid on side effects caused by the death of microfilariae, such as thrombosis, vasculitis or anaphylactic reaction, and supportive therapy should be warranted. In this case prednisolone has been given 60 min before the ivermectin treatment and a calcium heparin treatment has been started four days before and continued for twelve days after the ivermectin administration.

Use of Ivermectin in Amphibians

According to Clayton et al. (2012), ivermectin has been routinely used as an anthelmintic in amphibians at the National Aquarium, Baltimore. Ivermectin administration has been reported in amphibians and recommended dosages have included: 0.2–0.4 mg/kg p.o., s.c., i.m., topically; 2 mg/kg topically; and 10 mg/l as a 60 min bath. However, presumptive inadvertent overdose has occurred in dendrobatid frogs administered oral ivermectin via micropipette as part of a parasite management program. Within 48 h of administration, clinical signs consistent with ivermectin toxicity have been developed, including ataxia, flaccid paralysis, pulmonary respiratory depression, and total unresponsiveness to stimuli. Multiple frogs also have demonstrated generalized fluid accumulation consistent with hydrocoelom. Clinical signs have been developed in 31 frogs; 19/19 *Dendrobates auratus* and 12/29 *Dendrobates tinctorius*. Management has included fluid and nutritional support and calcium, antibiotic, and furosemide administration. The overall survival rate for frogs that developed clinical signs has been 32% (10/31). Of the 21 mortalities, seven frogs have been euthanized and 14 have been found dead. In surviving frogs, clinical signs have lasted up to three weeks, but have been mild after two weeks.

Use of Ivermectin in Fish

Fish acute toxicity tests have been carried out in Zebra fish (*Danio rerio*) and Catla fish (*Catla catla*) to assess the comparative tolerance to ivermectin induced toxicity and pathological alterations (Thiripurasundari, Sathya, Uma, Srinivasan, & Rajasekar, 2014). The animals have been exposed to various concentrations of ivermectin (1, 3, 5, 7 and 9 µg/l) and observed for behavioral changes in swimming pattern, maintaining equilibrium, pigmentation and mortality at various time intervals (24, 48, 72 and 96 h). The brain and the liver samples have been collected from the experimental fishes every 24 h for histopathological analysis. The behavioral changes and mortality in fishes have increased with the increase in ivermectin concentration and exposure time. Neurotoxic (gliosis and neuron degeneration) and hepatotoxic changes (necrosis and acute hepatitis) have been observed in the brain and liver of Zebra fish respectively when have been exposed to 7 µg/l of ivermectin for 96 h. In Catla fish, the same concentration of ivermectin has induced neuronal degeneration and necrosis in brain and hepatotoxic signs (hepatic cell degradation, vacuolations) in liver at 24 h exposure. The authors have concluded that Zebra fish is more tolerant to higher concentrations and prolonged exposure to ivermectin compared to Catla fish.

Samae (2015) has tested the efficacy of ivermectin in Zebra fish infected with capillariids and has established that ivermectin has eradicated the infection just after two administrations

(twice during a day). The author has compared efficacy of ivermectin with that of other dewormers and has shown that the treatment with ivermectin has been successful with the smallest therapeutic effort.

Some Cases of Using other Macrocyclic Lactones

Finally, aiming to add the present review we are including some cases of use of other macrocyclic lactones in captive animals.

D'Agostino et al. (2007) specify that parasitism is common in wild and captive amphibians. However, pharmacologic data are lacking for anthelmintic drugs. That is why these authors have performed a study to determine the influence of selamectin after topical administration in bullfrogs. Thirty-two adult American bullfrogs (*Rana catesbeiana*) have been randomly assigned into eight groups of four with each group representing a different collection time point. Seven groups have received selamectin (6 mg/kg) topically and the remaining group has served as the untreated control group. One group of frogs has been euthanized and blood samples immediately have been collected on days 0 (control), 1, 5, 10, 15, 20, 25, and 30. Plasma has been analyzed for selamectin using high performance liquid chromatography with fluorescence detection. Individual samples have been analyzed then data have been reported as the mean of the four frogs at each time point. A histologic evaluation of the lung, liver, kidney, and skin tissues has been performed and none of the frogs have shown histologic evidence of toxicity due to selamectin administration. The results have shown that bullfrogs appear to absorb selamectin very efficiently, concentrations reach high levels in the plasma, and there have been no apparent histologic effects from single dose administration.

In their publication Shaw et al. (2011) point that another amphibian – Archey's frogs (*Leiopelma archeyi*) is first on the list of evolutionarily distinct and globally endangered species. They also notice that captive breeding is an important strategy for protection of the species, but programs are hampered by a lack of information on diseases present in wild and captive populations. Two novel nematodes (*Koerneria* sp. and *Rhabditis* sp.) have been found separately in four captive Archey's frogs showing clinical signs of hemorrhagic purulent nasal discharge and weight loss. One of these frogs also has had a novel protozoal infection (*Tetrahymena*) in the nasal cavity. The authors have recorded that one frog has been treated successfully with oral moxidectin at 0.4 mg/kg for the nematode infection and topical metronidazole at 10 mg/kg for the protozoal infection. The clinical signs have abated only after both infections have been cleared.

As it has been pointed by Gelis et al. (2011), attempts to treat birds parasitized by *A. cantonensis*, *Brachylecithum podargi*, *Allodapa suctoria*, *Trichostrongylus* sp., *Leucocytozoon* sp. and unidentified cestodes with ivermectin (200 µg/kg i.m. daily for five days) or oxfendazole-praziquantel have been unsuccessful. However, at the same time the authors have treated another bird with a combination of steroidal and non-steroidal anti-inflammatory therapy followed by moxidectin (200 µg/kg i.m., then p.o. at the same dose once daily for four days) and the bird steadily has been recovered, such that by six weeks post presentation its ability to perch, grasp, fly and judge distances has been considered normal and it has been subsequently released.

Lobetti and Caldwell (2012) have recorded a case which highlights the potential for doramectin toxicity in lions (*Panthera leo*). Ten lions have been treated with a single injection of doramectin at a dose ranging between 0.2 mg/kg and 0.5 mg/kg and have showed clinical signs consistent with avermectin toxicity, namely ataxia, hallucinations, and mydriasis. Two subsequently have died whereas the other eight lions recovered after four to five days with symptomatic therapy. Post-mortem examinations of the two that died have shown cyanosis, severe pulmonary edema, pleural effusion, and pericardial effusion, with histopathology not revealing any abnormalities. In both these lions, doramectin brain and liver tissue concentrations have been elevated. According to the authors doramectin is regularly used in wild felids. That is why the potential for its toxicity have not to be ignored.

Hahn, D'Agostino, Cole, and Kukanich (2014) have evaluated the pharmacokinetic parameters of topical selamectin using healthy Helmeted guineafowl (*Numida meleagris*) housed at the Oklahoma City Zoo. For that purpose all birds have received one dose of 20 mg/kg selamectin topically. No adverse effects have been detected after the treatment. Based on the results, authors have concluded that selamectin may be a valuable antiparasiticide in some avian species.

Discussion

We have summarized the bigger part of the above given data in tables (Tables 1A–C, 2 and 3). Hope, in that form information is more convenient for looking up by the readers.

The summing-up and analyses of all of the literature data give us grounds for drawing the following conclusions:

- Herbivorous of the orders Artiodactyla and Perissodactyla represent the most frequently reported captive animals which have been treated with ivermectin. In them the drug has been used mainly for treating nematodoses. In gastrointestinal ones the most often applied dosage has been 200 µg/kg. The dosages of the cases of pulmonary helminthoses and extrapulmonary protostrongylidoses have been higher. No side effects have been observed during the ivermectin treatment in any doses in these mammals.
- The use of ivermectin for treating different parasitoses in elephants with doses varying between 100 and 400 µg/kg has been successful. The drug in dose 200 µg/kg has been also successfully applied in Red pandas. However, no expected results have been achieved in kangaroos. In them ivermectin has been much less effective against strongylid nematodes than has been reported for domestic herbivores.
- In monkeys ivermectin has been used in doses between 200 and 1000 µg/kg without side effects. In Raccoons the dosages have varied between 200 and 2000 µg/kg. However, the success of the cure has been relative in these two groups of animals and has been dependent on the species of the parasites.
- In carnivores, ivermectin has been used for treating nematodoses, mainly in dose 200 µg/kg. It has been reported about good effectiveness of the drugs, even in pulmonary parasitoses. No side effects have been observed.

Table 1A. Comparative data about ivermectin treatment in some zoo and captive wild mammals.

Animals	Parasites	Dosage and Scheme of Treatment	Results and Conclusions	Authors
Antelopes	<i>Nematodirus</i> , <i>Trichuris</i> , <i>Trichostrongylus</i> , <i>Ostertagia</i> , <i>Cooperia</i> , <i>Haemonchus</i> , <i>Chabertia</i>	Ivomec s.c. or Eqvalan i.m. 200 µg/kg (respectively 1 ml/50 kg and 1 ml/100 kg)	Cure infection, but nematode ova have reappeared in the feces after 6 months and a second dose of 0.7–1.0 ml/animal has given full cure. No side effects.	Frolka and Roštinská (1985)
Bactrian camel	<i>Trichuris</i>	Ivomec s.c. at 200 µg/kg (1 ml/50 kg)	The treatment has been ineffective against heavy infection. No side effects.	Frolka and Roštinská (1985)
White-tailed deer	<i>Parelaphostrongylus tenuis</i>	100 µg/kg	It not has a practical application for the elimination or prevention of infestations. Routine use may prove advantageous in temporary reducing the number of larvae shed in the feces of infected deer, thus minimizing environmental contamination with first stage larvae.	Kocan (1985)
Deer, Antelopes	<i>P. tenuis</i>	600 µg/kg i.m.	Initial mild improvement, but eventually all animals either have died or have been euthanized through complicating of the disease.	Nichols et al. (1986)
Gazelles	<i>Trichuris</i> , <i>Ostertagia</i> , <i>Cooperia</i> , <i>Trichostrongylus</i> , <i>Nematodirus</i> , <i>Strongyloides</i>	200 µg/kg s.c.	There have been marked decreases in the amount of eggs being shed and the number of animals shedding eggs of these nematodes.	Abaigar et al. (1995)
Mouflons	<i>Muellerius capillaris</i> , <i>Nematodirus</i> spp., <i>Oesophagostomum</i> spp.	200, 600, 1000 µg/kg s.c.	A dose of 600 µg/kg b.w. ivermectin as optimum for parenteral treatment of mouflon nematodoses has been recommended.	Lamka et al. (1997)
Antelopes, Soay sheep, Ibex, Deer, Elks	Different parasites	200 µg/kg p.o. for three days, applied three times in 5-wk intervals	The early-season program with ivermectin has resulted in very low to zero egg shedding in gazelle, adult Soay sheep, Ibex, Red deer, and Nelson's elk during the entire grazing season, but has failed to prevent high shedding in October in Arabian oryx and Scimitar-horned oryx.	Goossens et al. (2006)
Gazelles	<i>Nematodirus spathiger</i>	200 µg/kg s.c.	Reduction in mean fecal egg counts between 94% and 97.2%.	Mohammed et al. (2007)

Table 1B. Comparative data about ivermectin treatment in some zoo and captive wild mammals.

Animals	Parasites	Dosage and Scheme of Treatment	Results and Conclusions	Authors
Shetland ponies	Strongyles, <i>Parascaris equorum</i>	Eqvalan 200 µg/kg i.m.	Free of infection at fortnightly fecal examinations for three months. No side effects.	Frolka and Roštinská (1985)
Zebras	Intestinal strongyles	Medicated food pellets (containing 10 mg of ivermectin per kg)	The drug has shown an efficacy of 100% for up to 78 days post-treatment.	Lia et al. (2010)
Ponies	<i>Cyathostoma</i> sp.	400 µg/kg p.o.	It has been highly effective on the cyathostome infection. <i>O. equi</i> has been resistant.	Scháňková et al. (2013)
Wild ruminants	<i>Oxyuris equi</i>	200–400 µg/kg	Its efficacy in the fight against the pulmonary helminthoses has been better when applied at higher doses such as 400 µg/kg b.w. and in its s.c. and pour on administration.	Panayotova-Pencheva et al. (2015)
	Gastrointestinal and lung nematodes	400 µg/kg	Its effect has been incomplete.	
Kangaroos	Extrapulmonary protostrongyli-doses	Strongyles	200 µg/kg s.c.	Cripps et al. (2013)
Elephants	Variety of parasites	200–400 µg/kg p.o.	It has been much less effective against strongylid nematodes in kangaroos than has been reported for domestic herbivores. Appropriate for eliminating many types of parasites in elephants, and could minimize development of parasite resistance.	Gandolf et al. (2009)
Elephants	Microfilariae	10 mg/ml (1%) s.c. – dosage of 1 ml/100 kg	Single dose not only reduce the density of microfilariae in elephant's peripheral blood but also significantly decrease gastrointestinal nematodes. It is effective for the clearance of microfilaria for up to three months. Therefore the drug should be administered four times per year to elephants.	Oo et al. (2009)

Table 1B. (Continued)

Animals	Parasites	Dosage and Scheme of Treatment	Results and Conclusions	Authors
Red pandas	<i>Dirofilaria immitis</i> , <i>Baylisascaris ailuri</i>	200 µg/kg	No side effects have been observed. It has been successfully used to control and prevent heartworm disease in Red pandas.	Lan et al. (2012)
Monkey	<i>Edesonfilaria malayensis</i>	200 µg/kg i.m.	17 days after treatment, during a surgery (two hours after routine inhalation anesthesia), the monkey has died due to complications following the death of parasites.	Kornegay et al. (1986)
Monkeys	<i>Brugia malayi</i>	200–1000 µg/kg	Single doses have reduced the microfilarial counts by 59.9–89.6% of initial counts, four weeks after treatment. No serious side effects.	Mak et al. (1988)
Capuchin monkeys	<i>Filariopsis arator</i>	–	Not effective.	Lee et al. (1996)
Monkeys	<i>Congylonema</i> spp.	290 µg/kg p.o., once a week for four consecutive weeks	Clinical signs have been decreased; the drug has been safe with no adverse effects.	Adkesson et al. (2007)

Table 1C. Comparative data about ivermectin treatment in some zoo and captive wild mammals.

Animals	Parasites	Dosage and Scheme of Treatment	Results and Conclusions	Authors
Raccoons	<i>Placoconus lotoris</i> , <i>Capillaria putorii</i> , <i>Physaloptera</i> sp. <i>Capillaria plica</i> <i>Baylisascaris</i> <i>procyonis</i> , <i>Capillaria</i> <i>procyonis</i>	200–2000 µg/kg	Effective at all doses. Effective at higher doses (>600 µg/kg). Incompletely effective even at 2000 µg/kg.	Hill et al. (1991)
Raccoons	<i>B. procyonis</i>	1000 µg/kg given once	Seven days after the end of treatment no roundworms have been detected. Can be used at the dose rates tested in a deworming program for captive Raccoons.	Bauer and Gey (1995)
Gray wolves	<i>Dirofilaria immitis</i> , <i>Ancylostoma</i> <i>caninum</i> , <i>Toxocara</i> <i>canis</i>	200 µg/kg s.c. + 50 µg/kg monthly for 18 months	Effective in the elimination of <i>D. immitis</i> microfilariae, <i>A. caninum</i> , and <i>T. canis</i> , without any adverse tissue reactions, and has been effective for prophylaxis of heartworm and hookworm administered at 50 µg/kg monthly.	Kreeger et al. (1990)
Silver foxes	<i>Crenosoma vulpis</i>	200 µg/kg s.c.	Clinical signs have been resolved, and fecal exams have been negative at three and six week post treatment. No adverse reactions to the drug have been observed.	Conboy and Adams (1995)
Felidae, Canidae, Viverridae	<i>Toxascaris leonina</i>	“Oramec-drench”, MSD, Agvet-Holland 2.5 ml/kg	In addition to direct flaming of the floor and troughs it has been effective, even in case of persistent infections.	Sayid and Mohammed (1997–1998)

Table 1C. (Continued)

Animals	Parasites	Dosage and Scheme of Treatment	Results and Conclusions	Authors
Leopards	<i>Ancylostoma</i> spp.	200 µg/kg i.m.	Safety and quite efficacious in this case.	Suresh et al. (2000)
Panthers	<i>Ancylostoma</i> spp.	200 µg/kg i.m.	100% effective and seem to be the good drugs of choice to control worm burdens.	Singh et al. (2006)
Cheetahs	<i>Ancylostoma</i> spp.	Single injection (10 mg, Ivomect, Merial Inc., Duluth, Georgia, 30096, USA)	Eleven days later negative sample for the presence of parasite eggs.	Meny et al. (2012)
Lions	<i>T. leonina</i> , <i>Ancylostoma</i> spp.	300 µg/kg p.o.	It has reduced the fecal egg count of <i>T. leonina</i> and <i>Ancylostoma</i> spp. to 100% on 3rd day post treatment and may be recommended for the treatment of these infections.	Dehuri et al. (2013)
Hedgehogs	<i>Crenosoma lophocara</i> <i>Capillaria exigua</i>	200 µg/kg 200–400 µg/kg	100% effective. This parasite species has not been controlled even by a second treatment.	Matevsky and Mutafova (1987)
Fruit bats	–	One drop of 1% ivermectin topically	In some of the animals – sudden generalized paresis and other symptoms of toxicosis, death.	DeMarco et al. (2002)

Table 2. Comparative data about ivermectin treatment in some zoo and captive wild birds.

Animals	Parasites	Dosage and Scheme of Treatment	Results and Conclusions	Authors
Anatidae Cockatoos	<i>Echinuria uncinata</i> Haematozoa, microfilariae	200 µg/kg s.c. Two i.m. injections 1450 µg/kg	It has improved the condition of the birds. Effective in treating the microfilarial infections but the effect on the <i>Plasmodium</i> infection has not been determined.	Kock et al. (1987) Murata (1990)
Emus	<i>Baylisascaris</i> sp.	200 µg/kg p.o.	Treatment of clinical cases has had equivocal results. Weekly prophylactic treatment may prevent neurogenic migration of this parasite.	Suedmeyer et al. (1996)
Prairie falcon	<i>Serratospiculoides amaculata</i>	200 µg/kg p.o.	The condition of bird has been improved only for a short period. Not effective.	Hawkins et al. (2001)
Falcons	<i>Serratospiculoides</i>	1000 µg/kg s.c. repeated one or two weeks later	Without observing any detrimental effects.	Samour and Naldo (2001)
Falcons	<i>Serratospiculum seurati</i>	1000 µg/kg	Ivermectin can be effectively used in the protocol of therapy of the disease.	Tarello (2006)
Falcons	capillariids	2000 µg/kg i.m.	10–15 days later, the eggs of capillariid parasites have been disappeared, in association with complete clinical recovery.	Tarello (2008)
Pigeons	Nematodes	200 µg/kg s.c.	The efficacy of the drug has been 100%.	Basit et al. (2006)
Andean Cock of the Rock	<i>Thelazia anolabiata</i>	200 µg/kg i.m.	The bird has been in good health after the treatment.	Elias et al. (2008)
Frogmouths	<i>Angiostrongylus cantonensis</i> , <i>Brachylecithum podargi</i> , <i>Allodapa suctoria</i> , <i>Trichostrongylus</i> sp., cestodes, <i>Leucocytozoon</i> sp.	200 µg/kg i.m. daily for five days	Attempts to treat birds have been unsuccessful.	Gelis et al. (2011)

Table 3. Comparative data about ivermectin treatment in some zoo and captive reptiles.

Animals	Parasites	Dosage and Scheme of Treatment	Results and Conclusions	Authors
Red-footed tortoises	Intestinal nematodes	Single i.m. injection 400 µg/kg	Animals have been found in a state of extreme paresis or flaccid paralysis.	Teare and Bush (1983)
Leopard tortoise	Intestinal nematodes	25–300 µg/kg	The leopard tortoise has appeared to be the most susceptible, mild paresis has been developed with a dosage of 25 µg/kg. Death has occurred with dosages as low as 300 µg/kg. Some pareses have been observed.	Teare and Bush (1983)
Eastern box tortoises, Red-eared turtles	Intestinal nematodes	50–100 µg/kg		
Red-footed tortoises	<i>Proatractis</i> sp. <i>Kalicephalus</i> sp.	50 µg/kg	A dosage of 50 µg/kg has been found to be safe in red-footed tortoises, provided that treatment has not been repeated at intervals of less than seven days. However, adult parasites have not been disappeared after the treatment.	
Corn snake	–	400–1000 µg/kg	Safe.	Teare and Bush (1983)
Dumerils monitor	–	400 µg/kg	Safe.	
Snakes, Tortoise <i>Testudo graeca</i>	<i>Kalicocephalus viperae</i> <i>Hexametra</i> sp.	200–400 µg/kg s.c.	100% effective against <i>K. viperae</i> in snakes. <i>Hexametra</i> sp. in the snakes and in tortoise has not been controlled.	Matevsky and Mutafova (1987)
Chameleon	<i>Foleyella furcata</i>	Single dose – 200 µg/kg s.c.	Serious adverse reactions. Recommendation of avoiding ivermectin treatment of chameleons infected with <i>Foleyella</i> .	Széll et al. (2001)
Chameleon	<i>F. furcata</i>	Monthly treatment with low doses (10 µg/kg)	The microfilaremia has been markedly reduced after the first treatment and virtually disappeared after the second administration of the drug and the patient has been improved dramatically. Adulticidal effect, however, is not sure.	Bielli (2007)

- According to the literature data, some parasites in mammals are difficult to cure with ivermectin. Such are brain and tissue worms (for example *Parelaphostrongylus* sp., *Elaphostrongylus* sp.), some trichurids (*Trichuris* sp., *Capillaria* sp.) and oxyurids (*O. equi*). The only ones of the mammals in which serious side effect, including death, have been marked after the ivermectin use are bats.
- The most often dose of ivermectin used in birds has been 200 µg/kg. In some cases the treatment has been successful, in others – equivocal. The results have depended on the dosages, parasite species, and kind of the infections. In falcons higher dosages of the drug have been applied (1000–2000 µg/kg) without detrimental effects and treatments have been successful even in the cases of parasitism with *Serratospiculoides* sp. and capillariids.
- The experience of veterinarians with reptiles has shown that tortoises and chameleons are susceptible to ivermectin treatment. A treatment could be administered only in certain animal species at very low doses that without, however, guarantee of the adulticidal effect of the remedy. The ivermectin medication of other reptiles as *Dumerils monitor* and some snakes has been effective and safe even in dosages of 400–1000 µg/kg.
- Ivermectin has been successfully used in some amphibians and fish. However, the data in this respect suggest that if, in the case of undertaking such a treatment, the dosage and time of exposition of the animals to the action of ivermectin are not strictly observed, side effects including death, arise.
- Ivermectin has been administrated at different ways – p.o., s.c., i.m., topically, individual or collective, direct or indirect. Approach has been chosen depending on the facility of its applying in the specific animal species. Some peculiarities have been observed – ivermectin efficacy in the fight against the pulmonary helminthoses has been better when the drug has been applied s.c. or topically compared to p.o. When parasitic problems have been due to *Nematodirus* species direct administration to individual animals has been recommended.
- The zoo and other captive wild animals inhabit limited areas. That is why the geohelminthoses are widely distributed among them. In order to achieve a more durable effect of the ivermectin, measures should be taken for disinfection of the living area aimed at the destruction of the sexual products of the parasites that could become a source of new infections. Besides, schemes for preventive treatment should be worked out using in that respect experience of the various animal species and parasites targeting a maximum efficiency together with minimizing the threats of resistance development.
- The cure of filariid infections should be very careful and always accompanied with adequate anterior and concomitant therapy aiming to avoid possible complications from the death of adult parasites. Complications should be also considered if animals possibly harboring filariid nematodes are treated with ivermectin.
- Ivermectin has affected adult filaries in lesser degree. Its effectiveness has been better on microfilaries. That is why in the beginning of treatment it is advisable to administer other preparations against adult parasites and later to go on with the application of a scheme for preventive treatment with ivermectin at low doses.
- Ivermectin has been more effective in comparison with: mebendazole and levamisole in gazelles with gastrointestinal parasites; pyrantel pamoate and levamisole in lions with *Toxascaris leonina* and *Ancylostoma* spp.; thiabendazole and piperazine in lions with

Toxascaris leonina; other anthelmintics in cervids with gastrointestinal and lung nematodes; benzimidazoles in parasitized captive wild ruminants; oxfendazole and piperazine in wild pigeons; other dewormers in parasitized fish. However, it has not been effective in monkeys parasitized by lungworms *Filariopsis arator* and it has been with very low effect on strongylid nematodes in kangaroos. In these cases the parasites have been successfully affected by albendazole.

- Some studies about the use of other drugs from the group of the ivermectin (macrocyclic lactones) in captive animals have been found. They have shown that selamectin and moxidectin have been successfully applied in some amphibians, birds and mammals. In Red pandas parasitized by heartworms the ivermectin has been preferred instead of selamectin, because ivermectin has been more convenient for long-term prophylaxis without necessary to anesthetize the animals before its oral administration. Also, it has been cleared that doramectin may be potentially toxic for wild felids.

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