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HAYVANLARDA İMİDOKARB KULLANIMI

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ÖZET. İmidokarb dipropionat karbanilid türevi antiprotozoon ilaçtır. İlacın hayvanlarda kullanımı kenelerle nakledilen babesiosis (piroplasmosis) ve anaplasmosis tedavisinde onaylanmıştır. Ancak kenelerle nakledilen diğer bazı mikroorganizmalara etkinliği de araştırılmıştır. Sığır, at, eşek, katır, köpek ve koyunlar hedef türler olarak tanımlanmakla birlikte, diğer evcil ve yabani hayvanlarda da kullanılabilmektedir. İlacın tek doz olarak kullanımı önerilmekle birlikte, gerektiğinde 2-3 gün sonra uygulama yapılabilir. İlacın terapötik indeksi dardır ve dozaj rejimine dikkat edilmelidir. Bu derlemede imidokarbın hayvan türlerinde kullanımı, tedavide başarısı ve yan etkileri hakkında bilgiler verilmeye çalışılmıştır.

Anahtar Kelimeler: İmidokarb, hayvan türleri, kullanımı.

IMIDOCARB USE IN ANIMALS

ABSTRACT. Imidocarb dipropionate is a carbanilide derivative antiprotozoan drug. The drug is approved for use in animals for the treatment of tick-borne transmitted babesiosis (piroplasmosis) and anaplasmosis. However, its effectiveness against some other microorganisms transmitted by ticks has also been investigated. Although cattle, horses, donkeys, mules, dogs and sheep are defined as target species, they can also be used in other domestic and wild animals. Although it is recommended to use the drug as a single dose, it can be applied 2-3 days later if necessary. The therapeutic index of the drug is narrow, and attention should be paid to the dosage regimen. In this review, it could be tried to give information about the use of imidocarb in animal species, its success in treatment and its side effects.

Keywords: Imidocarb, animal species, usage.

Makale atıf

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INTRODUCTION

Imidocarb dipropionate is a carbanilide derivative aromatic diamidine. It has been stated that the drug has different mechanisms of action. It is thought to act by inhibiting the entry of inositol into protozoan-containing erythrocytes or by inhibiting the use/production of polyamines (EMA, 2001). Imidocarb is used in the treatment of babesiosis (piroplasmosis) and anaplasmosis in animals. In both infections, the blood parasite is created by the protozoan and the agents are transmitted by ticks. Cattle, horse, donkey, mule, dog and sheep have been identified as target species for which imidocarb is used. The drug is administered to horses, mules and donkeys at 2.4 mg/kg (Intramuscular-IM), cattle 1.2-3 mg/kg (IM), sheep 1.2 mg/kg (IM) and dogs 2.25-4.5 mg/kg (Subcutan-SC) once. If necessary, the second application can be made after 3 days since the therapeutic index of the drug is narrow, attention should be paid to the dosage regimen. It can be used together with oxytetracycline or doxycycline to increase the effectiveness of treatment. As side effects, cholinergic effects such as increased salivation, tremor, and cough can be observed. To prevent the occurrence of these side effects, atropine can be administered before the drug is administered. It has been reported that it can be used in pregnant cattle and horses. The drug has approximately 7 licensed commercial products offered for sale in Turkey (Yazar, 2018; Yazar, 2021a; MSD, 2022). In the continuation of the review, brief information about the use of imidocarb in animal species has been tried to be given.

USE in ANIMAL SPECIES

Cattle

After applying imidocarb 3 times with an interval of about one month to 2307 cows in total, it was determined that the animals generally tolerated the drug well, and it rarely caused mild and temporary side effects (increased salivation, diarrhea, tremor, ataxia, and excitement). It is stated that in the treatment of infections transmitted by ticks, it is necessary to prevent the transmission of the agent by first performing ectoparasitic treatment. It has been reported that the ectoparasitic drug should be applied at 15-day intervals to ensure the eradication of ticks before they reach the maturation period in their life cycle (Barre et al., 2011). In the toxicity study performed in calves, it was stated that the drug was administered at doses of 0, 5, 10 and 20 mg/kg (IM), local reactions were observed, and drooling, nasal discharge, respiratory distress, and diarrhea were observed depending on the dose. At the highest dose, kidney and liver necrosis and death were reported (Adams et al., 1980).

It has been reported that imidocarb in the treatment of babesiosis in cattle is not equally effective against different types of babesiosis (Gray and Potgieter, 1981). In the study, in which the effectiveness of imidocarb on immunity in cattle was carried out, it was determined that higher antibody formation was achieved with imidocarb application one week before FMD vaccination in calves (Afifi et al., 2014). Although it is thought that babesiosis infection is observed in hot months when ticks are active, it has been reported that it can also be observed in winter. A case report states that in February, a cow experienced reduced feed intake, stagnation, high fever, icteric mucosal and hemoglobinuria. It was stated that the diagnosis of babesiosis was made in the blood smear. It has been reported that imidocarb is used in the treatment and can be observed in the winter of the disease (Şahal et al., 2009). It has been reported that administration of imidocarb, oxytetracycline and vitamins to 20 cattle naturally infected with *Babesia bigemina* did not cure all patients and some died (Esmaeilnejad et al., 2021).

It has been reported that the efficacy of oxytetracycline is higher than imidocarb in cattle naturally (Atif et al., 2012) or experimentally (Sarli et al., 2021) infected with *Anaplasma marginale*. However, in another experimental study with *Anaplasma marginale* in calves, it was reported that imidocarb was more effective than tetracyclines (Mishra and Sharma, 1979). It has been reported that superoxide dismutase and catalase levels increase, while acetylcholine esterase and adenosine deaminase levels decrease after imidocarb administration to naturally infected cattle with *Anaplasma marginale* (Doyle et al., 2016).

The efficacy of imidocarb in cattle was also investigated in infections other than babesiosis and anaplasmosis. *Mycoplasma wenyonii* (*Eperythrozoon wenyonii*) is a blood parasite that settles in erythrocytes and causes deformations. It causes bovine eperythrozoonosis infection in cattle. Patients present with anemia, edema of the breast and hind legs, fever, lymphadenopathy, and decreased milk yield and weight loss. It has been stated that imidocarb at a dose of 3 mg/kg (IM, again after 2 days) can

be used in the treatment of the disease (Yan et al., 2008). It was stated that diminazen and isometamidium treatments in cattle experimentally infected with *Trypanosoma vivax* cured all patients, while imidocarb was not effective (Bastos et al., 2020). The effectiveness of imidocarb against some protozoa has also been studied in vitro. *Besnoitia besnoiti* is a protozoan species that causes skin infection in cattle. It has been determined that imidocarb has no activity in the in vitro cell line (Jiménez-Melendez et al., 2018).

Horse

Babesiosis in horses can be peracute, acute or chronic. The use of imidocarb is licensed in the treatment of babesiosis and anaplasmosis in equidae (horse, mule, donkey) as well as in cattle (Ekici and Işık, 2011; Yazar, 2018). In the pharmacokinetic study performed with 2.4 mg/kg (IM) administration in horses, it was determined that the C_{max} level was 0.39 mcg/ml, the T_{max} time was 1.16 hours, and the elimination half-life was 5.14 hours (Belloli et al., 2002). It has been reported that glycopyrrolate (0.0025 mg/kg, IV) is more effective than atropine (0.02 mg/kg, IV) in preventing the cholinergic side effects caused by imidocarb in horses (Donnellan et al., 2013). It has been stated that the drug can be used in pregnant horses (MSD, 2022). It has been reported that imidocarb was administered to prevent abortions observed in piroplasmosis infection in mares, and after administration, drug levels similar to those in maternal blood were detected in fetal blood (Lewis et al., 1999). It has been reported that changes in renal function parameters were observed after imidocarb administration of the drug to healthy ponies at a dose of 4 mg/kg (IM) 4 times with an interval of 3 days (Meyer et al., 2005). In the toxicity study performed in horses, imidocarb was administered 2 times 0, 2, 4, 8, 16 and 32 mg/kg (IM) with one day interval, followed by 21 days. In the study, the LD50 dose was determined to be approximately 16 mg/kg. In addition, it was stated that liver and kidney function parameters changed depending on the dose (Adams, 1981). In addition, it has been reported that the dose to be administered can be divided into two and administered with an interval of half an hour in order to prevent the formation of side effects caused by imidocarb in horses (Ionita et al., 2018). It has been reported that intravenous butylscopolamine bromide (0.2 mg/kg) + metamizole (25 mg/kg) combination can be used to prevent the side effects of imidocarb (2.4 mg/kg, IM) in horses (Abutarbush et al., 2013).

In horses with babesiosis, loss of appetite, fever, weakness, increased respiratory rate, anemia, pallor of the mucous membranes, conjunctivitis, dark yellow urine are observed. When imidocarb at a dose of 4 mg/kg (IM) was administered 4 times with an interval of 3 days, it was stated that the patients recovered (Rashid et al., 2009). It has been reported that fever, anorexia, tachycardia, icterus, edema and depression were observed in a horse infected with *Babesia caballi*, imidocarb (4 mg/kg, IM) was administered in the treatment, but the patient had to be euthanized, and acute renal failure was observed at autopsy (Adam et al., 2017). In another study, fever, weight loss, anemia, tachycardia, respiratory distress, lacrimation, anemia, erythrocytopenia, low hematocrit and tick presence were detected in a foal infected with Babesia caballi, and it was reported that the patient recovered after 2 weeks with imidocarb (2.2 mg/kg, IM, 2 times with a 24-hour interval), ivermectin and supportive treatment (Ememe et al., 2018). It has been stated that when imidocarb is administered to horses experimentally infected with *Babesia caballi* at a dose of 4 mg/kg (IM) 4 times with an interval of 3 days, it is effective in the treatment, and such aggressive imidocarb applications can be made when necessary (Schwint et al., 2009). *Babesia equi* is called Theileria equi in the new definition (Mehlhorn and Schein, 1998), and together with *Babesia caballi*, it is defined as one of the two most important factors in equine babesiosis (Ekici and Işık, 2011). In horses, *Babesia caballi* and *Babesia equi* are often isolated as the causative agents of babesiosis, and in some cases both are observed, and it is recommended to perform primarily imidocarb and oxytetracycline (5.5 mg/kg, IV, at least 2 days) as well as liquid-electrolyte therapy in the treatment (Brüning, 1996). It was stated that their carriers could not be prevented after the administration of high dose imidocarb (4.7 mg/kg, IM, 5 times with a 3-day interval) in 2 horses in which both factors were observed (Butler et al., 2008). Anorexia, anemia, fever and tachycardia were observed in a Theileria equi infected horse, and imidocarb was used at a dose of 2.2 mg/kg (IM, 2 times with a 24-hour interval) in the treatment, and 4.4 mg/kg (4 times with an interval of 3 days was used on the seventh day of the treatment, together with the diagnosis of the agent by PCR. It was reported that the patient had

swelling and mild colic at the infection site, and flunixin and butylscopolamine (0.3 mg/kg, Intravenöz-IV) was administered for colic (Dirks et al., 2021).

Donkey

In donkeys with babesiosis, fever, loss of appetite, pallor or jaundice in the mucous membranes, depression, difficulty in breathing, edema of the head and eyelids, increased pulse and respiratory rate, hemoglobinuria and lymphadenopathy are observed. Deaths are observed within the first 1-2 days in peracute cases and within 2 weeks in acute cases. Imidocarb is used in the treatment. Imidocarb dihydrochloride should never be used in donkeys (Ekici, 2021; Uslu et al., 2021). It has been reported that the drug was effective in the first few days after administration of imidocarb to donkeys experimentally infected with Babesia equi, but the donkeys died two months later as re-infected. It has also been reported that the drug causes hepatotoxicity in donkeys (Kumar et al., 2003).

Dog

Dogs with babesiosis present with stagnation, fever, enlarged spleen, jaundice, lymphadenopathy, anemia, keratitis, convulsions, hemoglobinuria, acute renal failure, thrombocytopenia, lymphopenia, and neutropenia. Often ticks are also detected on dogs (Máthé et al., 2006; Yazar, 2021b). Imidocarb is approved for use in the treatment of babesiosis in dogs. Different dosage regimens of the drug are reported. It has been reported by the FDA that 6.6 mg/kg of imidocarb can be administered intramuscularly or subcutaneously, and the second dose can be administered two weeks later if necessary. The drug should not be administered intravenously (Baneth, 2018). Pain at the injection site, drooling, runny nose, vomiting (Baneth, 2018), local reactions and anaphylaxis (Collett, 2000) can be observed as side effects in dogs. In order to prevent these general side effects, atropine (0.05 mg/kg) can be administered first (Baneth, 2018). In the study, it was reported that 0.01 mg/kg (IV) atropine administration to dogs before imidocarb (6.5 mg/kg) administration prevented side effects (Panghal et al., 2009). Less common side effects may include difficulty breathing, restlessness, diarrhoea, renal tubular/hepatic necrosis, and injection site inflammation and ulcers (Baneth, 2018). It has been stated that it should be used with caution in dogs with nephropathy (Máthé et al., 2007). When administered at a dose of 5.5 mg/kg (IM) to healthy dogs, it did not have a significant effect on hemogram and liver enzymes (Olukunle et al., 2018), but when administered intravenously at a dose of 4 mg/kg, the dog died, congestion and edema in the lungs, enlargement and bleeding in the kidneys at autopsy observed (Abdullah et al., 1984). It has been reported that severe depression, tachycardia, cyanosis, hindlimb tremor, collapse, diffuse liver necrosis, and death were observed in the dog one day after the accidental administration of 10 times the recommended dose (Kock and Kelly, 1991).

In experimental studies with babesiosis, it was stated that a single dose of imidocarb (6 mg/kg) protected dogs against *B. canis* for up to 8 weeks, and 5 mg/kg (once a day-SID) doxycycline administration improved the treatment (Irwin, 2009). It is stated that imidocarb, fluid-electrolyte therapy and blood transfusion may be the most successful treatment options in dogs with babesiosis (Irwin and Hutchinson, 1991). It has been reported that in dogs experimentally infected with Babesia canis, the patients recovered completely with imidocarb application, the parasites were eradicated, but the antibody level was found to be low in the treatment group, and the patients may be susceptible to reinfection (Brandão et al., 2003). In a study conducted in a dog infected with Babesia vulpes, it was stated that the administration of imidocarb (7.5 mg/kg, SC, once), atovaquone (13.3 mg/kg, oral-PO, 3 times per day-TID) and azithromycin (10 mg/kg, PO, SID) failed in the treatment and the patient had to be euthanized (Radyuk and Karan, 2020). It was reported that a dog infected with *Babesia gibsoni*, who had anemia and increased liver enzymes, died despite the administration of imidocarb (5 mg/kg, SC) and supportive treatments (metronidazole, prednisolone, doxycycline, liquid-electrolyte) (Irizarry-Rovira et al., 2001). It is stated that severe anemia and thrombocytopenia are observed in dogs naturally infected with *Babesia microti*-like piroplasm (*Theileria annae*). In treatment, imidocarb (5 mg/kg, SC, 2 times with a 2-week interval), atovaquone (13.3 mg/kg, PO, TID, 10 days) + azithromycin (10 mg/kg, PO, SID, 10 days) or buparvaquone (When 5 mg/kg, IM, 2 times with a 2-day interval) + azithromycin (10 mg/kg, PO, SID, 10 days) applications were compared, it was stated that the efficacy of imidocarb alone in the treatment was not good and the other two options should be evaluated (Checa et al., 2017). It has been reported to be effective when imidocarb (6 mg/kg, SC, 2 times with a 2-week

interval) is used in the treatment of dogs with the same effect (Simões et al., 2011). In a dog infected *with Babesia canis rossi*, stagnation, anemia, respiratory distress, fever, thrombocytopenia and leukopenia were observed, 9 mg/kg (IM) imidocarb was used first in the treatment and 8.3 mg/kg (IM) was used two weeks later and the patient recovered (Allison et al., 2011).

Anaplasmosis is observed in dogs in two forms. The causative agents belong to the rickettsia group and are transmitted by ticks. In the first form, the agents (*Ehrlichia platys*) settle on the platelets and are called canine thrombocytic anaplasmosis, while in the second form, the agents (*Anaplasma phagocytophilum*) settle into the neutrophils and are called canine granulocytic anaplasmosis. In the treatment, it is recommended to use imidocarb (two times with an interval of 2 weeks) together with doxycycline (10 days) (Yazar, 2021b). It was stated that the patients recovered with the administration of imidocarb (5.5 mg/kg, IM, 2 times 2 weeks apart), dexamethasone (0.5 mg/kg, IM), amoxicillin (7 mg/kg, SC, SID, 4 days) and liver-protecting amino acids to dogs with anaplasmosis infected with *Anaplasma phagocytophilium*, and this protocol can be applied in the treatment (Borisov et al., 2017).

Ehrlichiosis agents are transmitted to dogs by ticks. It occurs in two forms in dogs. *Ehrlichia canis* infects monocytes and macrophages and causes canine monocytic ehrlichiosis, while *Ehrlichia ewingii* infects granulocytes and causes canine ganulocytic ehrlichiosis. In the treatment, it is recommended to use imidocarb (two times with an interval of 2 weeks) together with doxycycline (10 days) (Yazar, 2021b). Studies have been conducted on the efficacy of imidocarb and tetracyclines alone or in combination in the treatment of ehrlichiosis. However, similar results were not found in these studies. Although it has been reported that the administration of doxycycline with or without imidocarb to dogs with ehrlichiosis is effective (Sato et al., 2020), its use alone is insufficient in the treatment, since imidocarb (6.6 mg/kg, IM, 2 times with a 2-week interval) cannot completely clear the agent (Eddlestone et al., 2006). When the effectiveness of imidocarb (5-7 mg/kg, IM, 2 times with a 2-week interval) and tetracycline hydrochloride (66 mg/kg, PO) is compared, imidocarb is 81% effective and tetracycline is 25% effective (Price and Dolan, 1980). In addition, in a study investigating the efficacy of oxytetracycline, doxycycline and imidocarb in the treatment, it was found that imidocarb was more effective than tetracyclines (Xaxa and Kumar, 2018) and doxycycline (10 mg/kg, PO, SID, 4 weeks), imidocarb (5 mg/kg, IM, 2 weeks interval). When the efficacy of the combined use and combined use were compared, it was reported that all three administration methods gave similar clinical results (Sainz et al., 2000).

Monocytosis, loss of appetite, vomiting, stagnation and polydipsia were observed in a dog infected with *Hepatozoon canis*, imidocarb (6 mg/kg, SC) was administered 3 times with one week intervals, and the agent was not observed in the blood 2 weeks later (Lilliehöök et al., 2019). In addition, case reports indicate that imidocarb (4 mg/kg, IM, 3 months with a 15-day interval), prednisolone (1 mg/kg, PO, twice a day-BID, 4 weeks), vitamins and fluid therapy (Marchetti et al., 2009) or imidocarb (5 mg/kg, SC) and doxycycline (5 mg/kg, PO, BID, 15 days) administration reported to be effective (Da Silva et al., 2011). When imidocarb (5-6 mg/kg, SC, 6 times at intervals of 1 week) and toltrazuril + emodepside treatments are compared in dogs naturally infected with *Hepatozoon canis*, both applications are not sufficient in the treatment (De Tommasi et al., 2014). Doxycycline (10 mg/kg, PO, SID) + imidocarb (6 mg/kg, PO, SID, 2 times with a 2-week interval) was administered to a dog puppy naturally infected with *Hepatozoon canis*, but the patient had to be euthanized 2 months later (De Bonis et al., 2021). It has been reported that imidocarb treatment is insufficient to eliminate the causative agent in dogs naturally infected with *Hepatozoon canis* (Sasanelli et al., 2010). It has been reported that the treatment efficacy of the combination of imidocarb (6 mg/kg, SC, 2 times with a 2-week interval) or imidocarb (6 mg/kg, SC, 2 times with a 2-week interval) + toltrazuril (10 mg/kg, PO, SID, 5 days) in dogs naturally infected with *hepatozoon canis* is similar (Pasa et al., 2011).

In some cases, it has been reported that more than one different factor may cause the infection. Diarrhea, polydipsia, anemic mucosal, increased respiratory and heart rate, anemia, thrombocytopenia, hyperbilirubinemia and increased liver enzymes are observed in dogs infected with *Babesia canis vogeli, Ehrlichia canis* and *Anaplasma platys*. It was observed that there was treatment after doxycycline (10 mg/kg, PO, BID, 4 weeks) and imidocarb (6.6 mg/kg, IM, 2 times with a 2-week interval) administration in the treatment

(Al Izzi et al., 2013). In another case report, it was stated that *Ehrlichia canis* and *Hepatozoon canis* were detected, *Anaplasma phagocytophilum* could also be found, and depression, anorexia, anemia, thrombocytopenia, fever and lymphadenopathy were observed as symptoms. It was reported that the patient's treatment was provided with doxycycline (5 mg/kg, PO, BID, 14 days) and imidocarb (5 mg/kg, SC, 2 times with a 2-week interval) (Mylonakis et al., 2004).

In a case report, it was stated that fever, anemia, jaundice, increased liver enzymes, loss of appetite and prolongation of coagulation time were observed in a dog with rangeliosis caused by *Rangelia vitalii*, which was transmitted by ticks. It was stated that after the administration of atropine (0.05 mg/kg, SC) in the treatment, imidocarb (6 mg/kg, IM) administration was successful (Borras et al., 2020).

Dogs infected with *Rangelia vitalli* show anemic mucosal symptoms, fever, anemia, and thrombocytopenia. It has been reported that imidocarb (5 mg/kg, SC, one time), prednisolone (2 mg/kg, PO, BID, 3 days) and doxycycline (5 mg/kg, PO, BID, 3 days) were used in the treatment of the disease, but some died (França et al., 2010).

Cat

Symptoms such as low fitness, anorexia, inactivity, fever, abdominal pain, and tick infestation were observed in a cat with hepatozoonosis caused by *Hepatozoon felis*, which was transmitted by ticks. It was stated that the patient recovered after administration of imidocarb (6 mg/kg, SC, again after 2 weeks) + doxycycline (5 mg/kg, PO, BID, 4 weeks) in the treatment of the disease (Basso et al., 2019).

Since fever, anorexia, and depression were observed in cytauxzoonosis infection caused by *Cytauxzoon spp*. in a cat, it returned to normal within the first week after imidocarb (3.5 mg/kg, SC) administration, but became ill again one month later, so the drug was re-administered (Legroux et al., 2017). In addition, it has been reported that the patients recovered with doxycycline (10 mg/kg, PO BID-SID, 21 days) + imidocarb (5 mg/kg, IM, 2 times with a 2-week interval) administration in two cats with the same infection (Carli et al., 2014).

Sheep and Goat

In a pharmacokinetic study performed with imidocarb (4.5 mg/kg, IM) in sheep, it was determined that plasma and intra-erythrocyte drug concentrations were similar, reaching T_{max} in 4 hours and increasing to 7.9 mcg/mL (Aliu et al., 1977). It was determined that lactating sheep eliminated the drug faster than goats, but no dose change was required for efficacy. (Belloli et al., 2006). It has been reported that markers of heart damage (cTnI, CK-MB, LDH) increase after administration of imidocarb 2.5-3 times the recommended dose to sheep (Ulusan et al., 2016), and it can cause serious toxicities when administered at a dose of 9.6 mg/kg in sheep infected with *Babesia ovis* experimentally (McHardy et al., 1986). In a study conducted in healthy sheep, when the effects of 2.4 mg/kg (IM) imidocarb on hemogram, blood gases, biochemical, coagulation and oxidative status parameters were examined, it was stated that it could affect oxidative status and coagulation parameters (Ekici and Isik, 2012). It has been stated that 1.2 mg/kg (IM) imidocarb administration is very effective in the treatment of experimental babesiosis infection in lambs, and 2.4 mg/kg (IM) can be used for prophylactic purposes (Sevinc et al., 2007).

In a toxicity study in goats, salivation, diarrhea, anorexia, respiratory distress, pulmonary edema, kidney damage and death were observed after lethal dose 6.75 mg/kg drug administration (Corrier and Adams, 1976). In a toxicity study conducted in goats, when imidocarb was used at 6, 12, 18 and 24 mg/kg (IM) doses, no change was detected at the 6 mg/kg dose, and at other doses; respiratory-heart rate and defecation-voiding increased, as well as depression, incoordination, hepatotoxicity, nephrotoxicity and deaths were observed (Ali et al., 1985). It was determined that pharmacokinetic parameters of goats experimentally infected with *Escherichia coli* endotoxin, *Trypanosomu evansi* and *Infectious Bovine Rhinotracheitis virus* were different from healthy ones (Abdullah and Baggot, 1986).

Other Species

It has been reported that babesiosis and anaplasmosis infections in buffaloes can cause high rates of death if not treated, imidocarb and oxytetracycline can be used in the treatment, and tick control is required (Coşkun and Yazar, 2019). It has been determined that it is highly effective in treatment when used at a dose of 1.5 or 2 mg/kg (IM) in buffaloes (Shen et al., 1997).

In the study performed at a dose of 3 mg/kg (IM) in white-tailed deer, it was determined that the C_{max} level of the drug was 880 ng/ml, the T_{max} time was 38.63 minutes, the half-life was 7.73 hours, and it was generally rapidly dispersed and partially eliminated (Milnes et al., 2020). Two rein deer infected with *Babesia odocoilei* have fever, hemoglobinuria, and hemolytic anemia as symptoms. It has been reported that one died as a result of acute renal failure, and the other recovered with imidocarb (3 mg/kg, SC, IM, 1., 2., 6., 9. and 21. days) and supportive treatment (antibiotic, vitamin, fluid-electrolyte) administration (Bartlett et al., 2009). However, in a reindeer infected with *Babesia venatorum*, it has been reported that despite supportive treatment with imidocarb, no treatment could be provided (Novacco et al., 2019).

It is stated that a decrease in hemoglobin, hematocrit and erythrocyte counts was observed in a mountain goat with babesiosis, and no improvement was observed despite the application of imidocarb (8.5 mg/10 kg) in the treatment (Marco et al., 2000). It was also reported that hemolytic crisis, edema and anemia were observed in antelopes infected with *Babesia irvinesmithi Martinaglia*, 1.2 mg/kg (IM) dose of imidocarb was used in patients and it did not cause side effects (McInnes et al., 1991).

It has been reported that wolves (Chrysocyon brachyurus) diagnosed with babesiosis were treated with imidocarb (6.6 mg/kg, IM, 2-2.5 weeks apart) (Phair et al., 2012; Naor et al., 2019) and a fox with rangeliosis originating from Rangelia vitalii was treated with imidocarb (5 mg/kg, SC) and dexamethasone(0.25 mg/kg SC), but both wolves and foxes did not recover (Copat et al., 2019).

CONCLUSION and SUGGESTIONS

- Today, imidocarb remains the most effective drug that can be used in the treatment of babesiosis and anaplasmosis.
- Cattle, horse, donkey, mule, dog and sheep have been defined as target species in the drug.
- In order to increase the effectiveness of the treatment, oxytetracycline or doxycycline should be administered together with imidocarb, depending on the animal species.
- In the treatment of infections transmitted by ectoparasites, an ectoparasitic drug suitable for the animal species must be applied in addition to the primary drug.
- In addition, vitamins, nonsteroidal anti-inflammatory drugs and fluid-electrolyte therapy can be applied.
- The drug may also be effective against different blood parasites.
- Since the therapeutic index of the drug is narrow, attention should be paid to dose calculation and administration route.

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