Acta Veterinaria (Beograd), Vol. 63, No. 2-3, 279-290, 2013.

DOI: 10.2298/AVB1303279T UDK 616.993.1:616-08+159.944

CANINE BABESIOSIS TREATMENT WITH THREE DIFFERENT MEDICINES

TORBICA G*, BEDRICA LJILJANA**, SAMARDŽIJA M**, LIPAR MARIJA**, LJUBOJEVIĆ DUBRAVKA***, KRESZINGER M** , ĐURIČIĆ D**** and HARAPIN I**

*Veterinary practice Samobor, Samobor, Croatia**
*Faculty of Veterinary Medicine, Zagreb, Croatia***
*Veterinary practice „Fiziovet", Zagreb, Croatia****
*Veterinary Practice Đurđevac, Đurđevac, Croatia*****

(Received 10th January 2013)

Canine babesiosis is a relatively frequent disease in Croatia. Elevated body temperature, anemia and haemoglobinuria are the most common signs. Diagnosis is rapidly obtained by employing blood smears, as B. canis is present in the red blood cells of affected dogs. Treatment is favourable and without consequences. Blood work was performed initialy, prior to treatment, and on the 1st and the 7th day following treatment. Following history and examination of the dogs blood and urine samples were taken. After confirmation of B. canis in the red blood cells, alltogether 226 dogs were tretated. Out of them 80 were tretaed with Berenil® (diminazen aceturate, Hoechst), 72 were tretated with Imizol® (imidocarb dipropionate, Schering-Plough-Animal-Health) and 74 with Oxopirvedin® (fenamidine dizetionate, Merial). Clinical findings, haematological analysis and urine analysis are given and statistically assesed. After tretment with Berenil®, symptoms of babesiosis regressed within 24 hours. Health improved more slowly in the group treated with Oxopirvedin® in comparioson with the group treated with Berenil®. Contrary to the above, Imizol® displayed the slowest regression of the disease and reinfestation with B. canis within 30 days was not noted. That is not the case if treatment was provided by Berenil® and Oxopirvedin®. In all 226 cases of canine babesiosis side effects were not noted, except topically inflammed tissue at the site of subcutaneous application.

Key words: antiparasitic drugs, babesiosis, dogs, treatment

INTRODUCTION

Babesiosis is one of the most common diseases in Croatia. The number of involved dogs is increasing constantly. The disease appears during the whole year period, with frequent outbreaks in the spring and autumn. Canine babesiosis can vary from peracute and fatal to chronic and subclinical, depending on microbial virulence and host resistency. Canine babesiosis affects dogs, wolves,

coyotes and jackals. Canine babesiosis is manifested with a variety of symptoms but some of them sometimes are not related to babesiosis. Besides, there can be persistent chronic infestation with babesia in the case when in the periferal blood smear babesiae were not found. Those animals have continuously increased antibody titers, and some demonstrate nonspecific signs of chronic infection (Bedrica *et al.*, 1998).

Today in Croatia there are two medications registrated for canine babesisiosis tretament: *Imidokarb* (Imizol®) and *Phenamidin* (Oxopirvedin®). Since 90ties Berenil® had been used also in canine babesiosis tretment. Thus, we decided to determine if there was a difference in the rate of recovery on the basis of up to date results. *Babesia canis* is a causative agent of canine babesisosis, and there are three subtypes of large babesia classified as: *B. canis canis, B. canis vogeli* and *B. canis rossi*. These three subtypes are morphologicaly idetical (Fabisiak *et al*., 2010). Mediators in the transmission are ticks from the family *Ixodidae* (Lobetti, 2005).

Signalment. Caninine babesios has varying clinicals signs which depend on pathogenity, type and subtype of agent and age, body condition and general health of the host (Živičnjak, 2001). In most cases the typical signs of the diseases appear and outbrake abruptly. Elevated body temperature, distemper, anemia, jaundice haemoglobinuria and in some cases spleenomegaly appear (Ramadan *et al*., 1991; Boozer and MacIntire, 2003). Bohm (2006) described inapetence and weight loss.

Ramadan *et al*. (1990) in their research investigated 106 dogs affected with babesiosis and concluded that canine babesiosis manifested itself in many forms, from acute to chronic and with different clinical symptoms the are characteristic for certain forms. Peracute disease is rearly manifested and it is characterised by shock and death after 24 hours of anorexia and lethargy. The peracute form most often affects puppies (Breitschwerdt, 1984). The subclinical form of babesiosis probably appears even more often then it is detected because symptoms are not clearly defined and the agent is rarely observed in the blood smear. Clinical symptoms appear if involved dogs are under stress or treated with corticosteroids (Kuttler, 1988). When treated in time non complicated babesiosis survival rate is almost 100% (Harapin *et al*., 1999; Matjila *et al*., 2009). In the atypical form of babesiosis the simptoms are in accordance with heavy destruction of inner organs and secondary bacterial infection caused. Welzl *et al*. (2001) reported that the most often affected organs are the kidneys (Harapin *et al*., 1993; Lobetti, 2000; Vaughan-Scott, 2001), liver (Mathe i sur., 2006), lungs (Lobetti, 2000), central nervous sistem (Vaughan-Scott, 2001; Böhm, 2006; Jacobson, 2006; Ayoob *et al*., 2009) and muscles.

In affected dogs blood coagulation is disturbed (Lobetti, 2000) and very often acute pancreatitis is noted (Lobetti, 2006; Ayoob, 2009). Haematological parameters depend on geographic region and type and subtype of *B. canis* (Lobetti, 2005). The most common haematological findings are anemia and trombocytopenia (Scheppers, 2008; Köster, 2009). In the initial phase of the disease anemia is mild, normocytic, normochromic. With progression of the disease macrocytic, hypochromic and regenerative anemia appear (Fabisiak et

al., 2010.). Haemolitic anemia is regenerative and includes anisocytosis, polychromasia, reticulocytosis, normoblastemia and spherocytosis (Schoeman, 2009). Canine babesiosis is often the cause of tromocytopenia. There are differences in platelet count considering the parasitic infestation. Jacobson (2006) noted in South Africa that canine babesiosis causes severe thrombocytopenia in almost all affected dogs. Leucopenia is also a very common finding in canine babesiosis (Mathe *et al*., 2006; Solano-Gallego, 2009). The decreased number of neutrophils and lymphocytes in the blood is due to sequestration of WBC (white blood cells) in the spleen (Mathe *et al*., 2006). In canine babesiosis biochemical findings depend on the severity of the disease. In uncomplicated cases, usually there are no significant changes in serum biochemistry (Lobetti, 2005), whereas in complicated cases serum biochemistry reveals increased ALT (alanine aminotraspherase), ALP (alkaline phosphatase), Tbil (total bilirubine) and BUN (blood urea nitrogen) values (Manzillo *et al*., 2010). Urine analysis displays haemoglobinuria, bilirubinuria, proteinuria, and epithel cells originated from the kidneys (Schoeman, 2009).

Applied diagnostic methods in canine babesiosis are:

1. Presence of the parasite in the red blood cell (RBC) in blood smear – (Harvey *et al*., 1988; Comazzi *et al*., 1999).

2. PCR method – in chronic cases of babesiosis, the number of parasites in the peripheral blood cells. In a period of 10 days parasits dissapear from the cirlulation, thus it is possible to detect the disease only by DNA originated from babesia (Sobczyk *et al*., 2005).

3. Platelet count (Ayoob *et al*., 2009).

4. *In vitro* cultivation of babesia – this method is very reliable, but very expensive (Holman *et al*., 1993).

5. Immunological and serological examinations – imunological and serological examinations are characterised with high specifitiy and sensibility (Skotarczak, 2008). Very often serological examinations are unreliable in the initial stage of the disease as antibodies are not observed in the first 8-10 days after parasitic infestation (Comazzi *et al*., 1999).

6. Postmortal diagnostics. In acute canine babesiosis authopsy shows spleenomegaly, jaundice and edematous and haemoglobin stained kidneys. Subepicardial and subendocardial bleeding can be also found. At the incision site of the edematous and hyperemic spleen bleeding appears. The gallbladder is usually distented as a result of overfiling with dense bile (Fry and McGavin, 2008).

Treatment. Many antiparasitics are present on the market.

Imidocarb dipropionat. Imidocarb is an antiparasitic, antibabesic and antirickesia agent as it interferes with babesia nucleic acids metabolism (Sakar and Sakar, 1999).

Following imidocarb application rapid clinical emprovement appears in cases of uncomplicated babesiosis. Fever disappears at once or it decreases the following day, haemoglobinuric urine appears normal within 48 hours. Parasites dissapear from the erythrocytes within 2-3 days after imidocarb application. This was proven by the fact that spleenectomized dogs inoculated with blood

originating from dogs who were suffering from babesiosis and treated with imidocarb were not affected.

It has not been determined whether the cured dogs remain permanent carriers of babesia in the spleen, bone marrow and limph nodes (Mathe *et al*., 2006). In patients who have damaged liver and kidneys treatment with imidocarb should be with caution. Adverse reactions following imidocarb application in puppies, pregnant animals and animals in lactation were not noted (Plumb, 2005).

Combination of diminazen aceturate and phenazone is a powerful antiprotoozic chemotherapeutic that is well tolerated by animals (Sakar and Sakar 1999). However, diminazen does not eliminate the parasites from the canine body (Schoeman, 2008).

Tripan blue in 1% solution is the oldest medicine against babesiosis which is still in use all round the world (Schoeman, 2009). It does not eliminate the parasites, but reduces their number. Tripan blue should be used in combination with imidocarb or diminazen (Kraje, 2001). Subcutaneous or intramuscular application incites the tissue (Lobetti, 2000). Three weeks after the initial application, the treatment can be repeated (Schoeman, 2009).

Fenamidin dizetionate is proven that can damage enzymatic systems which are responsible for polyamine (biogenic amines) metabolism in the host, and at the same time blocks DNA synthesis (Sakar and Sakar, 1999).

Acryflavin affects *Babesidea* protozoa and *B. canis*. The onset of action is rapid. Acryflavine is aggregated in RBC and destroys the parasites. Subcutaneous and intramuscular application causes severe local damage of the tissue (Delak, 1985).

There are antiparasitic agents such as: paraquon, pentamidin (Irwin, 2009), isometamidium, amicarbalid (Lehtinen, 2007), doxycylin, quinuronium sulfate (Ayoob *et al*., 2009). Doxycilin in doses of 10 mg/kg of body weight q12 applied for 7-10 days decreases the number of parasites. If PCV in canine babesiosis is less then 15%, blood transfusion of whole blood is necessary (Lobetti, 2006).

Prophylaxyis. The most important factor is to protect the animals from tick infestation. Vaccination based on soluble antigen originated from *in vitro* culture of *B. canis* is unsufficient protection (Schetters *et al*., 2001).

MATERIAL AND METHODS

226 cases of canine babesiosis were included in this research. All dogs were divided into the three groups according to treatment. 17 dogs were treated with Berenil®, 74 with Oxopirvedin® and 72 dogs were treated with Imizol®. Berenil® was applied in doses of 3.5 mg diminazen per 1 kg body weight (b.w.) that was in 1 mL Berenil® per 10 kg body weight. Oxopirvedin® was applied in doses of 15 mg phenamidin per 1 kg b. w. Therapeutic range is relatively narrow, as 20 mg/b.w. could cause encephalopathy. Low concentrations of phenamidin in a large volume (approximately 1 mL of Oxopirvedin® per 1 kg b.w.) decrease the risk of overdosing. Imizol® was used in doses of 6 mg Imidocarb per 1 kg b.w. that is 0.5 mL Imizol® per 10 kg b.w.

Treated dogs were females and males at age of 4 months to 11 years. One or more ticks were found in 68% of affected dogs. The initial examination (0 day) was comprised of body temperature and blood sampling from the *v. cephalica antebrachii* in order to perform haematology tests, serum biochemistry, and blood smears. The hemogram was performed on automatic counter (Coulter type ZF) and RBC, Hgb and PCV were determined. Urine samples were also taken and hemoglobin was recorded from one plus to three pluses. Prior to initial treatment the body weight of each dog was measured.

After proving the presence of *B. canis* blood smears were stained by Pappeneheim solution within 90 minutes after smear preparation. All dogs received antiparasitic and supportive therapy if needed. The next day blood was resampled. The majority of patients improved in general health. Blood work was repeated 7 days after the initial treatment.

Statistical analyses between the groups were done by ANOVA (StatSoft, Statistica, 8.0) version and using the Tukey's tests post hoc analysis.

RESULTS

In Figures 1 to 5 are shown the obtained results for: body temperature, RBC, Hgb, PCV and presence of haemoglobin in urine in the 0, 1st and 7th day foregoing therapy with Berenil®, Oxopirvedin® and Imizol® for all groups.

Body temperature

In Figures 1. results for body temperature prior to, during and after the treatment are given at 0 day (prior to treatment) body temperature was significantly elevated ($p<0.05$). One day after initial treatment body temperature decreased siginificanty in all groups. Dogs treated with Berenil® had significantly

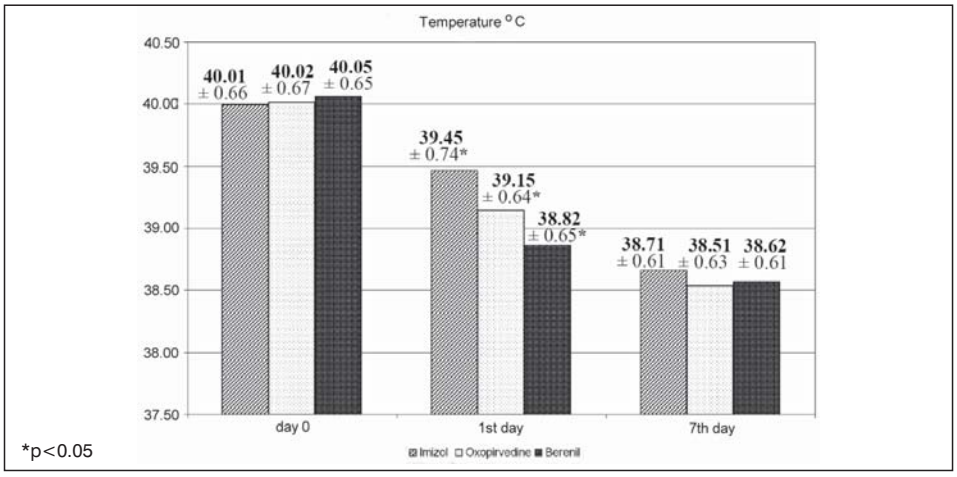

Figure 1. Body temperature prior to, during and after treatment

lower ($p<0.05$) body temperature in comparison to those treated with Oxopirvedin® and Imizol®. In Berenil® the active substance is a phenazone which is a nonsteroid antiinflammatory drug (NSAID). On the 7th day after inital treatment body temperature was within normal ranges in all groups and with no significant differences ($p>0.05$) between groups.

RBC count

Figure 2 displays the average RBC prior to, during and after treatment. In the first day after treatment with Oxopirvedin® and Imizol®, the RBCs were significantly lower in comaprison with the group treated with Berenil® ($p<0.05$).

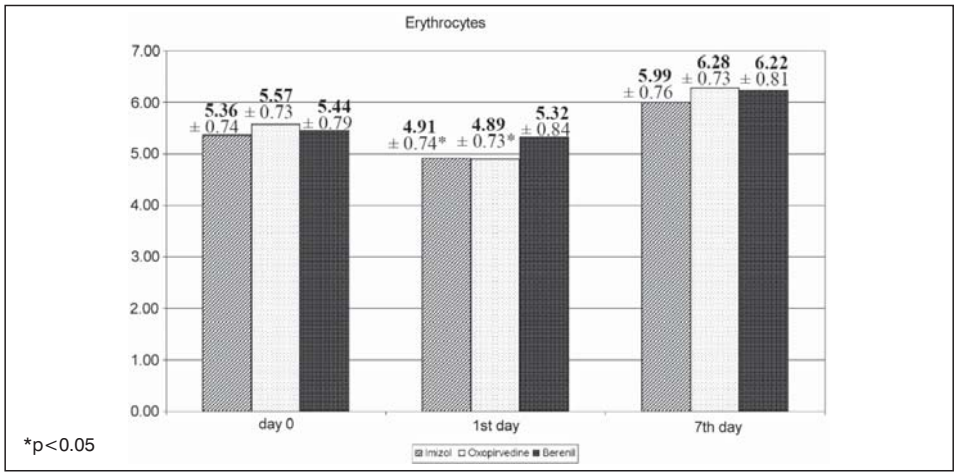

Figure 2. An average RBC prior to, during and after treatment

On the 7th day after treatemt RBC count was within the normal range in all groups. The increase of RBC was slower in dogs treated with Imizol®, but it was not of statistical significance ($p>0.05$).

Haemoglobin

Figure 3 shows an average haemoglobin concentration prior to, during and after treatment. In the initial testing Hgb was low in all groups, without significant differences between the groups ($p>0.05$). The first day after treatment Hgb concentration was significantly lower in the group treated with Imizol®. On the 7th day after treatment it was within normal ranges in all groups although in the Imizol treated group the rate of increase was slow.

Haematocrit

Figure 4 exhibits PCV prior to, during and after treatment. Prior to initial treatment a significant difference was noted between the groups ($p<0.05$). One day after inital treatment PCV decreased in comparison to initial analysis, but was significantly lower in the group treated with Imizol ($p<0.05$). On the 7th day after

treatment PCV values were within normal ranges in all groups. The group treated with Imizol® reached normal ranges slower in comparison to other groups.

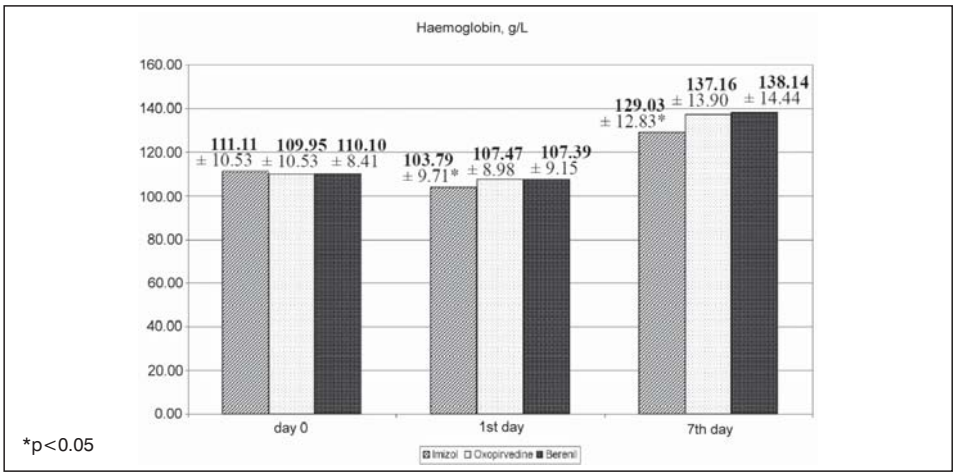

Figure 3. An average haemoglobin concentration prior to, during and after treatment

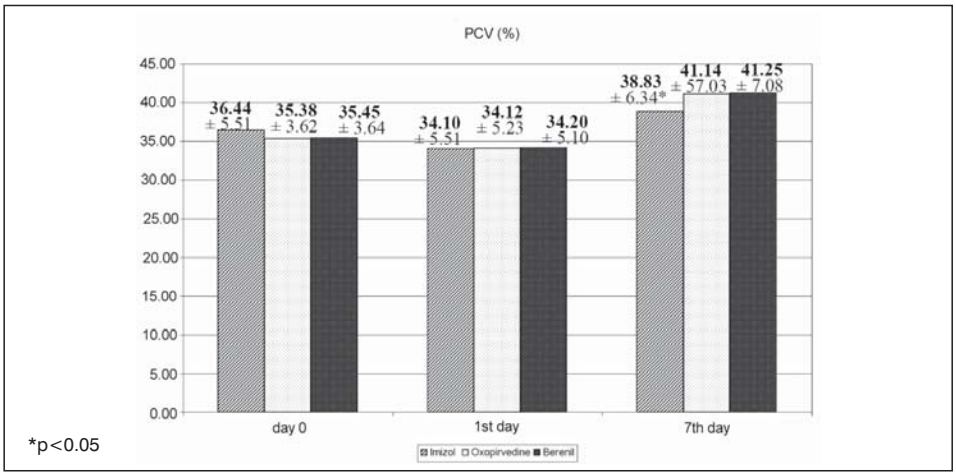

Figure 4. PCV prior to, during and after treatment

Haemoglobinuria

Figure 5 exhibits haemoglobinuria prior to initial treatment. Hemoglobinuria was present in 86% of dogs later treated with Berenil®, in 78% of dogs treated with Oxopirvedine® and in 89% of dogs treated with Imizol®. 24 hours following tretament haemoglobinuria decreased in all groups, but significantly only in the group treated with Berenil®. On the 7th day after treatment in all groups haemoglobinuria was not detected.

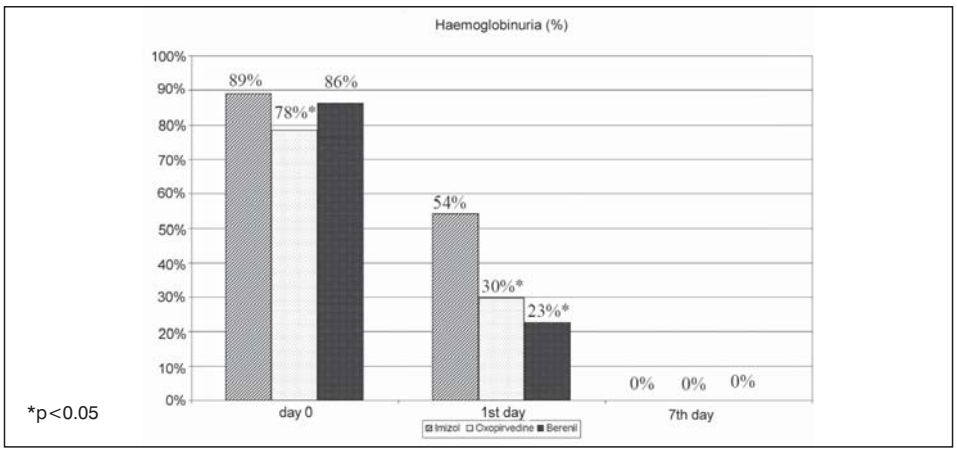

Figure 5. Presence of haemoglobinuria prior to, during and after treatment

In the period of 30 days after treatment owners reported on the course of reconvalescence. In dogs treated with Berenil® three cases of reinfestation with canine babesiosis were detected. In the group treated with Oxopirvedin® one case of canine babesiosis reccured. Berenil® and Oxopirvedin® were applied subcutaneously. Side effects were noted in 4 dogs treated with Berenil® and in 5 dogs treated with Oxopirvedin®, only local tissue inflammation at the application site was noted. In the group treated with Imizol® local inflammation at the site of sc. application was observed in 14 dogs. In 6 cases out of 14 seroma was described. Local inflammation spontaneously regressed, wherease seromas were tretaed surgically. Within 39 days three dogs died, pathological findings did not confirm babesiosis was the cause of exitus.

DISCUSSION

Fever and incresed heart rate are common findings in uncomplicated canine babesiosis (Lobetti, 2000; Vaughin-Scott, 2001; Bohm, 2006; Ayoob *et al*., 2009), that is in accordance with our research. In all three groups diagnosed with canine babesiosis on the initial day (day prior to treatment) elevated body temperature was measured. In the first day after treatment body temperature significantly decreased in all groups. In the group treated with Berenil® body temperature was significantly lower in comparison to groups treated with Oxopirvedin® and Imizol® ($p<0.05$). Berenil contains phenazone that is an antipiretic NSAID. On the 7th day after treatement in all groups body temperature was within the normal range without significant differences between groups.

Dollar (2011) confirmed in his research a significant correlation between body temperature and heart rate, and a significant correlation between body temperature and RBC count, PCV and platelet count. Ramadan and Bauer (1978); Harapin *et al*. (1993); Stojković *et al*. (1993) and Duh *et al*. (2004) confirmed that haemolytical anemia and trombocitopenia were the main findings in uncomplicated canine babesiosis.

In our research prior to any treatment RBC count was at the low border line in all groups. The first day after treatment RBC count was significantly lower in the groups treated with Oxopirvedin® and Imizol®. This could be explained as within 3-4 days after haemolysis there was no regeneration of RBC in the periferal blood samples because the haematopoetic system needs at least 4 days for RBC production. In dogs regenerative response begins at 4-7 days after the insult and comes back to normal values after 15 days, although mild anemia can be still present (Scheepers, 2008). On the 7th day RBC count was within normal ranges in all groups. The increase in RBC count was slower in the group treated with Imizol even though it was not significant ($p>0.05$). On the basis on this research fever anemia haemoglobinuria and weeknes are the main signs of canine babesiosis. Those signs dissappeared rapidly if treated with Berenil® and side effects were not noted. That was the reasons for treatment with Berenil®.

Losos and Crockett (1969) noted that Berenil® in doses of 30-35 mg/kg body weight cause spastic paresis and involuntary movement. Cases like the above mentioned pathoanatomically were analysed at the Faculty of Veterinary Medicine in Ibadan, Nigeria. Tadić *et al*. (1993) compared an outcome of babesiosis treatment with Berenil® and Imizol®. Authors concluded that the Imizol® was the best medicine for canine babesiosis although it had a slower resorption rate which was the reason for delayed recovery.

Signs of babesiosis dissapeare rapidly if treated with Oxopirvedin®, but slowly if treated with Berenil®. Imizol® is the treatment of choice for canine babesiosis or metaphylactic use.

Imidocarb is a medicine for babesiosis tretment, antiricketia treatment and chemoprophylactic use. In sensitive babesia distrurbs the sythesis of nucleic acids (Sakar and Sakar, 1999). After imidocarb application improvement is rapid in cases of uncomplicated babesiosis. Fever dissapears the next day, wherease haemoglobinuria disappears within 48 hours. Babesia are eliminated from RBC within 2-3 days after inital treatment. This was proven experimentally, blood was taken from treated animals and inoculated to spleenectomized dogs and babesiosis did not occour.

It was not clearly explaind if the cured dogs are permanent carriers of babesia in the spleen, bone marrow and lymph nodes (Mathe *et al*., 2006). Imizol® is also used in prophylaxis and it protects from recurring babesiosis for 30 days. Wercammen *et al*. (1996) supported that Imizol® has prophylactic properties on a daily basis by measurement of body temperature, parasitic infestation, haematological values and antibody titer. Simptoms regress rapidly following Berenil® application, slower regression was noted following Oxopirvedin® while Imizol® application resulted in the slowest regression of simphtoms (Bedrica *et al*., 1998). In grops treated with Berenil® and Oxopirvedin® three and one case of babesios reccurence were noted, respectively. It is doubtful if it was reinvasion with babesia or reinfection due to tick borne disease. Diminazen and phenamidine do not eliminate all babesia present in the host, a certain number of babesia can be still present in the spleen. Within four weeks after treatment with Imizol®, reccurence with babesia was not noted. Within 39 days three patients died, authopsy did not confirm babesiosis as a cause of death.

CONCLUSION

On the basis of conducted research babesiosis is characterised with fever, anemia, haemoglobinuria and weekness, if treated with Berenil® regression of symphtoms dissappear rapidly and side effects were not noted. Symphtoms of canine babesiosis regress rapidly if tretaed with Oxopirvedin®, Imizol® is the medication of choice for reccurent babesiosis and for metaphylactic use. Beside that Imizol® posseses prophylactic properties and protects the host for a time. The final conclusion is that all medication used in this research reached sufficiently significant results in canine babesiosis treatment.

Address for correspondence:
Prof. dr. Ivica Harapin, Full Professor, PhD, DVM
Faculty of Veterinary Medicine
University of Zagreb
Heinzelova 55
10000 Zagreb, Croatia
E-mail: harapin@vef.hr

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LEČENJE BABEZIOZE U PASA SA TRI RAZLIČITA LEKA

TORBICA G, BEDRICA LJILJANA, SAMARDŽIJA M, LIPAR MARIJA,
LJUBOJEVIĆ DUBRAVKA, KRESZINGER M, ĐURIČIĆ D i HARAPIN I

SADRŽAJ

Babezioza pasa je relativno česta bolest u Hrvatskoj, praćena vrlo visokom telesnom temperaturom, anemijom i hemoglobinurijom. Nakon brzo postavljene dijagnoze nalazom *B. canis* u krvnom razmazu, lečenjem se postižu dobri rezultati i ne izaziva posledice. Laboratorijske pretrage krvi rađene su prije davanja terapije (nulti dan), prvi i sedmi dan nakon terapije. Nakon utvrđivanja anamneze i kliničkog pregleda pasa, uzeti su uzorci krvi za hematološke pretrage i krvne razmaze. Također je napravljena i analiza urina. Nakon potvrđene dijagnoze nalazom *B. canis* u krvnim razmazima pasa, lečeno je ukupno 226 pasa, 80 ih je lečeno Berenilom® (diminazen aceturate, Hoechst), 72 su lečena Imizolom® (imidocarb dipropionate, Schering-Plough-Animal-Health), a 74 Oxopirvedinom® (fenamidine dizetionate, Merial). Rezultati kliničkih nalaza, hematoloških analiza i analiza urina su prikazani i statistički procenjeni. Nakon lečenja Berenilom®, klinički su se simptomi babezioze povukli relativno brzo, unutar 24 sata. Poboljšanje kliničkih simptoma nakon aplikacije Oxopirvedina®, nastupilo je sporije u usporedbi sa brzinom poboljšanja kliničkih simptoma nakon aplikacije Berenila®, ali brže u usporedbi sa brzinom poboljšanja kliničkih simptoma nakon apikacije Imizola®. Delovanje Imizola®, u usporedbi sa ostala dva navedena leka bilo je sporije, bez reinvazije babesia unutar 30 dana, što smo zapazili da se javlja nakon terapije sa Berenilom® ili Oxopirvedinom®. U sva 226 slučaja babezioze nisu se pojavile neželjene nuspojave, osim lokalne upale tkiva na mestu subkutane aplikacije navedenih lekova.