International Journal of Livestock Research, Vol. 10 (9) Sep' 2020
http://www.ijlr.org
eISSN: 2277-1964
NAAS Rating 2020 – 5.36

Original Research

Comparative Efficacy of Imidocarb Dipropionate and Oxytetracycline-Doxycycline Combination Therapy in Ehrlichia Infected Dogs

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How to cite this paper: Game, H., Waghmare, S., Pajai, K., Kuralkar, S., Hatzade, R., & Katre, R. (2020). Comparative Efficacy of Imidocarb Dipropionate and Oxytetracycline-Doxycycline Combination Therapy in Ehrlichia Infected Dogs. *International Journal of Livestock Research*, 10 (9), 74-80. doi: http://dx.doi.org/10.5455/ijlr.20200523020011

Received : May 23, 2020
Accepted : Aug 23, 2020
Published : Sep 30, 2020

Abstract

The present study was undertaken to evaluate the therapeutic efficacy of imidocarb dipropionate and oxytetracycline-doxycycline combination therapy on the basis of improvement in clinical, haemato-biochemical parameters in ehrlichiosis in dogs. Total 12 dogs positive for ehrlichia were selected for the study and randomly divided into 2 groups. First group of ehrlichia positive dogs was treated with oxytetracycline @ 22 mg/kg body weight intravenously for 3 days followed by doxycycline @ 10 mg/kg body weight orally for 21 days along with supportive therapy. Second group of 6 ehrlichia positive dogs was treated with two doses of Imidocarb dipropionate @ 6 mg/kg body weight intramuscularly at 14 days intervals along with supportive treatment. The study concluded that both the drugs found effective against ehrlichiosis in dogs along with improvement in clinical and haemato-biochemical parameters. However, imidocarb dipropionate demonstrated faster recovery on the basis of improvement in clinical and haemato-biochemical parameters than the long-term treatment with oxytetracycline – doxycycline combination therapy in ehrlichia infected dogs.

Keywords: Biochemical, Dogs, Doxycycline, *Ehrlichia canis*, Haematology, Imidocarb Dipropionate, Oxytetracycline

Introduction

Canine ehrlichiosis is an infectious fatal tick-borne disease caused by the rickettsia *Ehrlichia canis* (Harrus *et al.*, 1997). It has been reported throughout the world from both tropical and subtropical regions, causing extensive morbidity and mortality among domestic dogs and other canids (Shimon Harrus *et al.,* 1999). The disease is mainly characterized by high fever, depression, lethargy, weight loss, anorexia, ophthalmic lesions, splenomegaly, epistaxis, oedema in hind legs, emaciation and lymphadenopathy (Sainz *et al.*, 2000, Anuchai *et al.*, 2006). Principal hematologic abnormalities include thrombocytopenia, mild anemia and mild leukopenia during the acute stage, mild thrombocytopenia in the subclinical stage and pancytopenia in the severe chronic stage. The main biochemical abnormalities include hypoalbuminemia, hyperglobulinemia, and hypergammaglobulinemia (Harrus *et al.*, 1997). The treatment of ehrlichiosis includes administration of specific drugs viz. tetracycline, imidocarb dipropionate, chloramphenicol and amicarbalide. The penetration of the drug into cell is essential to eliminate the ehrlichia infection because it persists intracellularly. Therefore, lipid-soluble tetracyclines (doxycycline) should be given for a minimum period of 21-28 days (Neer *et al.*, 2002). There are several advantages lies in the treatment of the imidocarb dipropionate over tetracycline. The tetracycline treatment causes the problem of owner's compliance due to the long term oral antibiotic therapy. The high doses of tetracycline may cause vomiting in some dogs whereas the treatment with imidocarb is less dependent on the owner's compliance. However, several studies reported side effects of imidocarb dipropionate include salivation, dyspnoea, serous nasal discharge and diarrhoea (Matthewman *et al.*, 1994).

Considering the merits and demerits of the tetracyclines and imidocarb dipropionate, the present study was undertaken to assess the therapeutic efficacy of imidocarb dipropionate alone and oxytetracycline –doxycycline combination therapy in ehrlichia infected dogs on the basis of improvement in clinical, haemato-biochemical parameters.

Materials and Methods

In the present investigation total 12 dogs positive for ehrlichia based on Snap 4Dx Canine ehrlichia antibody test kit (IDEXX, USA) and blood smear examination were selected for the study. The selected dogs positive for ehrlichia were randomly divided into two groups, comprising of 6 animals in each group. Group I (T1) of 6 ehrlichia positive dogs was treated with oxytetracycline @ 22 mg/kg body weight intravenously for 3days followed by doxycycline (Doxt) @ 10 mg/kg body weight orally for 21 days along with supportive therapy. Group II (T2) of 6 ehrlichia positive dogs was treated with two doses of Imidocarb dipropionate (Babimido) @ 6 mg/kg body weight intramuscularly at 14 days intervals along with supportive treatment.

The haematological parameters *viz*. haemoglobin (Hb) (gm /dl), packed cell volume (PCV) (%), total leukocyte count (TLC) (x 10^3/cu.mm), total erythrocyte count (TEC) (x10^6/ cu.mm), differential leukocyte count. (DLC) (%) and platelets count (x 10^3/ cu.mm) were estimated on '0' day and 25th day after treatment by using ABX VETPACK automatic haematological analyser. The biochemical parameters viz. total serum protein (gm/dl), serum albumin (gm/dl), serum globulin (gm/dl), alanine transaminase (ALT) (IU/L), aspartate transaminase (AST) (IU/L), blood urea nitrogen (BUN) (mg/dl), serum creatinine (mg/dl) and total bilirubin (mg/dl) were estimated on '0' day and 25th day after treatment by using rapid diagnostic kits on the Star 21 Plus biochemistry auto analyser. The data obtained during the present study with respect to different biochemical parameters was analysed statistically by two-way factorial Design using software SPSS version 21.0 and WASP version 2.0.

Results and Discussion

In the present investigation, all 12 positive dogs for ehrlichiosis shown clinical signs such as pyrexia (91.66 %), dullness and depression (83.33%), lymphadenopathy (75%), splenomegaly (75%), anorexia (58.33%), inappetence (41.66%), ocular discharge (33.33%), corneal opacity (25%), epistaxis both unilateral as well as bilateral (16.66%), incoordination in hind limbs (8.33%) and pulmonary signs like coughing, sneezing, respiratory distress and moist rales (8.33%). The post treatment clinical recovery in dogs of both the groups is given in Table 1.The group (T2) treated with imidocarb dipropionate showed complete clinical recovery on 7th day post treatment, indicated 100% clinical recovery on 7th day post treatment, whereas 66.66% (4 dogs) and 100% clinical recovery was noted on 7th day and 15th day in the group treated with oxytetracycline followed by doxycycline, respectively (Table 1). The results of the present study indicated that the group treated with 2 doses of imidocarb dipropionate demonstrated

faster recovery without any side effects as compared to the group treated with oxytetracycline followed by doxycycline in dogs with ehrlichiosis. Roopali *et al.* (2018) and Xaxa and Kumar (2018) also reported the better and faster recovery with imidocarb dipropionate in ehrlichiosis infected dogs as compared to oxytetracycline and doxycycline.

Table 1: Post treatment clinical recovery in dogs of group T1 and T2

Groups	'0' day	3rd day	7th day	15th day
Group (T1)	6	1(16.66 %)	3 (4) 66.66%	2 (6) 100%
Group (T2)	6	2 (33.33%)	4 (6) 100%	(6) 100%

**Figures in parenthesis refer to total dogs recovered*

The imidocarb dipropionate has been preferred in the treatment of ehrlichiosis than tetracycline because it has many advantages over the tetracycline. However, sometimes the administration of this drug causes some side effects such as salivation, ocular discharge and depression after treatment. Hence, in the present study, injection Atropine sulphate @ 0.02 mg/kg BW was given in all the 6 dogs of group T2 before administration of imidocarb dipropionate to prevent these side effects. Many researchers have also reported side effects of imidocarb dipropionate treatment against ehrlichiosis (Wood, 1971, Price and Dolan, 1980).

In the present study, the faster recovery of Imidocarb dipropionate might be due to persistence of the drug for a longer period of time in plasma and tissues and therefore produces highly active concentration to destroy the intracellular ehrlichia organism. As it has long half-life in animals and only one or two dosages are required to eliminate the ehrlichia which persist intracellularly. The exact mechanism of action of imidocarb dipropionate is not known. However, many researchers reported that imidocarb dipropionate interfere with production or utilization of polyamines or it blocks the entry of inositol into the cell containing the parasite. The inositol is an important and essential nutrient into the cells thus leads to the starvation of organism. The other workers suggested that imidocarb dipropionate act directly on the parasite, resulted in alteration in number and size of nuclei and causes vacuolation in the cytoplasm (Xaxa and Kumar, 2018). The tetracycline needs to be given for a prolonged period of time which results in major problem with owner's compliances, whereas imidocarb dipropionate is less dependent on owner compliance as compared to tetracycline treatment. The longer duration of treatment with tetracycline may also cause vomition in dogs. The long-term therapy of tetracycline may stain the dental enamel of young dogs. Many workers reported the therapeutic efficacy of oxytetracycline and doxycycline given for a prolonged period of time against ehrlichiosis in dogs (Neer *et al.,* 2002 and Greene and Harvey, 1984).

In the present investigation haemato-biochemical parameters were studied to find out any alteration in these parameters associated with ehrlichiosis in dogs. The mean haematological and biochemical levels in group T1 and T2 on '0' day and 25th day post treatment is presented in Table 2 and Table 3, respectively. The haematology study demonstrated declined in haemoglobin, PCV and TEC in ehrlichia infected dogs before treatment (Table 2), as compared to normal reference range (Brar *et al*., 2014). Many researchers reported decline in Hb, PCV and TEC in ehrlichia infected dogs (Petrov *et al.,* 2018). The decline in Hb, PCV and TEC could be attributed to the loss of blood due to epistaxis, petechial, ecchymotic haemorrhages and hematemesis etc. as seen in dogs with ehrlichiosis. These haemorrhages seen in ehrlichiosis might be as a result of thrombocytopenia and disturbance in the haematopoietic system and bone marrow hypoplasia as a result of progressive replication of canine ehrlichiosis in the bone marrow, which leads to suppression in erythroid, myeloid and megakaryocytic cells resulted in decreased RBC production. (Abeygunawardena *et al*., 1990, Petrov *et al.,* 2018 and Roopali *et al.,* 2018). The mean Hb, PCV and TEC was improved on 25th day post treatment indicated effectiveness of both the treatment in improving Hb, PCV and TEC after treatment (Table 2). Many researchers also reported improvement in these parameters after treatment with imidocarb dipropionate, oxytetracycline and doxycycline in dogs with ehrlichiosis (Petrov *et al.,* 2018, Roopali *et al.,*2018). The mean TLC was slight low before treatment ('0' day) in dogs with ehrlichiosis (Anuchai *et al.,* 2006, Bhardwaj 2013). It might be due to decrease in lymphocytes as a result of myelosuppression in ehrlichiosis (Ettinger and Feldman, 2005). In both the treatment groups, the mean TLC was improved on 25th day post treatment.

In the present study, the mean platelet count was low before treatment ('0' day) in the dog with ehrlichiosis as compared to normal reference range documented by Brar *et al.* (2014), indicated thrombocytopenia (Chipde *et al.,* 2007, Kottadamane *et al.,* 2017, Petrov *et al.,* 2018 and Roopali *et al.,* 2018). The thrombocytopenia in ehrlichiosis

might be due to increased splenic sequestration of platelets, decreased half-life of circulatory platelets, suppressed production, platelets dysfunction and increased platelets destruction by anti-platelets antibodies (Pierce *et al.*, 1977, Kelly 2000 and Ettinger and Feldman, 2005). Both the treatments (imidocarb dipropionate and oxytetracycline-doxycycline therapy) showed improvement in the altered platelet count on 25th day post treatment (Petrov *et al.* (2018); Roopali *et al*., 2018; Xaxa and Kumar 2018).

Table 2: Mean values of haematological parameters in group T1 & T2 on pre-treatment ('0' day) and 25th day of post treatment

S. No.	Parameters	Groups	Intervals	
			Before Treatment	After Treatment
			'0' day	25th day
1	Haemoglobin (gm/dl)	Group (T1)	9.27±0.76	11.67±0.52
		Group (T2)	8.30±0.67	11.67±0.81
		Pooled mean	8.78±0.50^{a}	11.67±0.46^{b}
2	PCV (%)	Group (T1)	27.38±3.15	35.60±1.63
		Group (T2)	24.95±2.02	35.20±2.44
		Pooled mean	26.17±1.82^{a}	35.40±1.40^{b}
3	TEC (x10^{6}/cu.mm)	Group (T1)	4.30±0.67	5.91±0.32
		Group (T2)	3.90±0.29	5.96±0.19
		Pooled mean	4.10±0.35^{a}	5.94±0.18^{b}
4	TLC (x 10^{3}/cu.mm)	Group (T1)	7.42±1.52	10.38±1.51
		Group (T2)	6.32±1.35	8.45±1.22
		Pooled mean	6.87±0.98^{a}	9.42±0.97^{b}
5	Platelet count (x 10^{3}/cu mm)	Group (T1)	112.67±20.49	257.00±29.52
		Group (T2)	118.50±33.21	235.83±48.54
		Pooled mean	115.58±18.62^{a}	246.42±27.27^{b}
6	Neutrophils (%)	Group T1	57.83±3.37	66.83±0.48
		Group T2	53.67±2.70	63.33±1.69
		Pooled mean	55.75±2.15^{a}	65.08±0.99^{b}
7	Lymphocytes (%)	Group T1	37.17±3.98	27.33±1.05
		Group T2	35.33±1.74	28.67±0.99
		Pooled mean	36.25±2.09^{b}	28.00±0.72^{a}
8	Monocytes (%)	Group T1	2.33±1.02	2.83±0.65
		Group T2	7.67±1.43	5.83±1.22
		Pooled mean	5.00±1.16	4.33±0.80
9	Eosinophil (%)	Group T1	2.67±1.54	3.00±0.86
		Group T2	2.33±0.49	2.17±0.31
		Pooled mean	2.50±0.77	2.58±0.45

The differential leucocyte count study revealed reduction in neutrophils per cent, whereas slight elevation in lymphocyte per cent in dogs with ehrlichiosis before initiation of treatment (Kottadamane *et al.*, 2017, Xaxa and Kumar 2018). The mean eosinophils (%) and monocytes (%) were within the normal reference range. These altered neutrophils (%) and lymphocytes (%) per cent were improved significantly on 25th day post treatment over the '0' day (before treatment) in dogs with ehrlichiosis, irrespective of treatment groups (Table 2).

In the present study, the mean total serum protein (gm/dl) level was slightly higher on '0' day (before treatment) in ehrlichiosis infected dogs as compared to the normal reference range (5-7 gm/dl) (Brar *et al.*, 2014). Similar observations were also reported by Harrus *et al*. (1997), Saniz *et al.* (2000), Dubie *et al.* (2014) and Mylonakis and

Theodorou (2017). The increase in total serum protein level could be attributed to elevated globulins (Harrus *et al.*, 1998). The total serum protein level was improved significantly on 25th day post treatment irrespective of groups, indicated effectiveness of both the treatments in improving total serum protein level in canine ehrlichiosis (Table 3). The mean serum albumin level was slightly lower in dogs with ehrlichiosis as compared to a normal reference range (2.5 - 4.0 gm/dl) as documented by Brar *et al.* (2014). Many research workers reported decrease in albumin level in dogs with ehrlichiosis (Chipde *et al.*, 2007, Procajlo *et al.*, 2011, Smitha and Kumar 2014, Petrov *et al.*, 2018 and Roopali *et al.*, 2018), The decrease in albumin level in the present investigation might be the consequence of anorexia and peripheral loss of albumin through the oedematous inflammatory fluids as a result of increased vascular permeability (Woody and Hoskins 1991, Smitha and Kumar, 2014). The serum albumin level was improved on 25th day post treatment over the pre-treatment albumin level ('0' day) in respective groups (Roopali *et al.*, 2018).

Table 3: Mean values of biochemical parameters in group T1 & T2 on pre-treatment ('0' day) and 25th day of post treatment

S. No.	Parameters	Groups	Intervals	
			Before Treatment	After Treatment
			'0' day	25th day
1	Total serum protein (gm/dl)	Group (T1)	7.56±0.49	6.33±0.47
		Group (T2)	7.98±0.61	7.07±0.30
2	Serum Albumin (gm/dl)	Group (T1)	1.97±0.21	2.24±0.19
		Group (T2)	1.94±0.21	2.26±0.08
3	Serum Globulin (gm/dl)	Group (T1)	5.59±0.45	4.09±0.42
		Group (T2)	6.09±0.69	4.81±0.35
4	ALT (IU/L)	Group (T1)	42.02±8.95	34.49±8.55
		Group (T2)	41.06±4.95	36.12±4.17
5	AST (IU/L)	Group (T1)	42.48±6.76	39.72±6.02
		Group (T2)	38.67±3.23	34.33±2.77
6	BUN (mg/dl)	Group (T1)	29.10±5.20	20.62±2.54
		Group (T2)	31.07±6.19	18.73±1.62
7	Serum creatinine (mg/dl)	Group (T1)	1.39±0.12	1.02±0.13
		Group (T2)	1.72±0.49	0.89±0.07
8	Total bilirubin (mg/dl)	Group (T1)	0.32±0.05	0.25±0.04
		Group (T2)	0.34±0.04	0.28±0.03

The mean serum globulin level was slightly higher on '0' day (before treatment) in ehrlichiosis infected dogs, indicated hyperglobulinaemia in dogs with ehrlichiosis (Harrus *et al.*, 1997, Chipde *et al.*, 2007, Procajlo *et al.*, 2011, and Roopali *et al*., 2018). The increase in serum globulin level in ehrlichiosis might be due to committed B cell response to chronic antigenic stimulation by the infective organism indicating a prolonged duration of infection (Harrus *et al.*, 1997 and Roopali *et al*., 2018). Gamma globulin concentrations increase during the febrile phase of canine ehrlichiosis and persist during the subclinical and chronic phases of the disease (Ristic and Holland 1993). The serum globulin level was improved on 25th day post treatment as compared to '0' day globulin level in respective groups (Roopali *et al.*, 2018)

In the present study, the statistical analysis revealed non-significant variation in serum ALT and AST level in ehrlichiosis infected dogs and was within the normal range throughout the experimental period (Table 3). The BUN level was slightly higher on '0' day (before treatment) in ehrlichiosis infected dogs as compared to the normal reference range (8 - 25 mg/dl) documented by Brar *et al.* (2014). Similar findings were also reported by Chipde *et al.* (2007), Procajlo *et al.* (2011), and Roopali *et al.* (2018). The increase in BUN in canine ehrlichiosis might be due to immune complex-mediated glomerulonephritis (Harrus *et al.*, 1998). The altered BUN level was improved on 25th day post treatment over the pre-treatment ('0' day) level in respective treatment groups (Roopali *et al.*, 2018). The mean serum creatinine and total bilirubin level did not differ significantly and was within the normal range

throughout the study period (Table 3).

Conclusion

The study concluded that the treatment with imidocarb dipropionate alone and oxytetracycline-doxycycline combination therapy found effective in inducing complete clinical recovery along with improvement in haemato-biochemical parameters in treated dogs. However, two doses of imidocarb dipropionate demonstrated faster recovery on the basis of improvement in clinical and haemato-biochemical parameters than the long-term treatment with oxytetracycline–doxycycline combination therapy. Hence, imidocarb dipropionate can be a first choice of treatment against ehrlichiosis in dogs because of faster recovery, short duration of treatment and less dependency on owner's compliance than the treatment with oxytetracycline followed by doxycycline.

Acknowledgement

Authors are highly thankful to the Associate Dean of Post Graduate Institute of Veterinary and Animal Sciences, Akola, Maharashtra (India) for financial support and necessary permissions.

Conflict of Interests

There is no conflict of interest.

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