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Comparison of the Effects of Prednisolon, Danazol and Testosteron Propionat Therapy in Dogs with Immune Mediated Hemolytic Anemia and Thrombocytopenia

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Abstract: The purpose of the study was to determine and compare the effectiveness of Prednisolon, Danazol and Testosteron propionate in the treatment of 45 dogs with IMHA and IMT. All dogs were selected from dogs diagnosed IMHA and IMT at the Uludag University Faculty of Veternary Medicine, Internal Medicine Clinic, 2003 and 2007 years comprised the animal population of the study. Clinical, biochemical and hematological examination were performed to all dogs during 3 weeks. Dogs in the present study were divided into 3 groups which consisted of 15 dogs. Group I received prednisolone at immunosuppressive doses. Group II received Danazol and also group III received testosterone propionate. The mainly manifesting disturbances in presentation were exercise intolerans, pale mucous membranes, icterus, hemoglobinuria, petechiae and ecchymosis, melena and epistaxis. Hemoglobin and hematocrit levels were significantly higher in group I and II compared with group III at the end of treatment (P=0.05). Thrombocyte counts were within normal reference limits in group I and II at the end of the therapy. In conclusion in this study, despite the normal response to conventional treatment, prednisolone therapy and danazol as synthetic androgen, it was deterimined that there were no anticipated effects by testosterone propionate for treatment of AIHA in dogs.

Key Words: Anemia, platelet, erythrocyte, corticosteroids, androgen.

İmmun İlişkili Anemi ve İmmun İlişkili Trombositopenili (İT) Köpeklerde Prednisolon, Danazol ve Testosteron propionate'ın Ekinliğinin Karşılatırılması

Özet: Bu çalışma Prednisolon, Danazol ve Testosteron propionate'ın İmmun ilişkili anemi (İHA) ve immun ilişkili trombositopenili (İT) 45 köpeğin tedavisindeki etkinliğinin belirlenmesi ve karşılatırılması amacıyla yapıldı. Bütün köpekler 2003–2007 yılları arasında Uludağ Üniversitesi Veteriner Fakültesi İç Hastalıkları Kliniğiinde İHA ve İT tası konan köpekler arasından seçildi. Bütün köpeklere ait klinik, hematolojik ve biyokimyasal muayeneler 3 hafta boyunca yapıldı. Çalışmada kullanılan köpekler her biri 15 köpekten oluşan 3 gruba ayrıldı; 1. Gruba immunsupresif dozajda prednisolone uygulandı. 2. Gruba Danazol ve 3. Gruba testoterone propionate uygulandı. Köpeklerde ilk muayene sonuçları arasında solgun mukoz membranlar, ikterus, hemoglobinüri, peteşi, ekimoz, melena ve epistaksis saptandı. Hemoglobin ve hematkrit düzeyleri tedavi sonunda 3. grup hayvanlara göre 1. ve 2. gruptaki hayvanlarda istatistiki olarak daha yüksek olarak saptandı (P=0.05) Trombosit sayısı tedavinin sonunda 1. ve 2. Gruptaki hayvanlarda normal sınırlar içindeydi. Sonuç olarak, prednisolone ve danazol uygulamaları tedavide etkili olurken, testosterone propionate tedavisde etkili olmadığı belirlenmiştir.

Anahtar Kelimeler: Anemi, platelet, eritrosit, kortikosteroid, androjen.

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Introduction

Immune mediated hemolytic anemia (IMHA) and immune–mediated thrombocytopenia (IMT) are frequently encountered immunohematologic diseases[12,22,28] IMHA and IMT are defined as a reduction in the numbers of circulating erythrocyte and thrombocyte because of immunoglobulin or complement induced removal by the mononuclear phagocyte system, mainly in the spleen and liver[3,12].

Canine IMT and IHA typically present as spontaneous petechial and ecchymotic cutaneous and mucosal haemorrhagies, lethargy, weakness, pale mucous membranes, icterus, hemoglobinuria, and anorexia[7,12,18,28,38]. A diagnosis of IMHA requires one or more of the following three hallmarks has to be present to reach a definitive diagnosis of IMHA. It is included that marked spherocytosis, true autoagglutination and positive direct coombs' test[7,12,18,26,35]. Especially, presence of marked spherocytosis and true autoagglutination along with thrombocytopenia in the dog with anemia are virtually pathognomic of IMHA and IMT[12].

Although treatment with glucocorticoid drugs remains the mainstay of management of this disease, therapy with other agents has been reported to improve for control of the disease[6,15,24,36]. Numerous drugs including corticosteroids, azathioprine, danazol, chlorambucil, cyclosporine, cyclophosphamide and human immunoglobulin G have been used in the treatment of IMHA and IMT[6,12,15,24,28,34].

The aim of this study was to determine and compare the effectiveness of Prednisolon, Danazol and Testosteron propionate in the treatment of 45 dogs with IMHA and IMT.

Material and Methods

Animal Selection

Totally 45 dogs were selected serially from the dogs with IMHA and IMT that referred to the clinics of the Faculty of Veterinary Medicine in Bursa between 2002 and 2007. Blood sampling and treatments were performed in accordance with the Animal Welfare Guidelines. Routine clinical examination procedures were performed to all dogs. Criteria for inclusion of dogs in this study included a positive autoagglutination, marked spherocytosis, thrombocytopenia (<100.000/μL) and Hematocrit (Hct) (<32%). Cases with an identifiable underlying disease such as neoplasia, lymphoma, blood parasites (i.e. ehrlichiosis, babesiosis) were excluded from the study.

The dogs included in this study were of various body weights (mean 22 kg, range 5 – 41.5 kg), different breeds (10 mixed breeds, 9 German shepherds, 7 Cocker Spaniels, 6 Golden retrievers, 6 Doberman Pinchers, 4 terier, 3 Anatolian Shepherds), sex (28 males, 17 females) and ages (mean 4.5 years, range 2 – 9 years). All dogs in this study were previously vaccinated against rabies, distemper virus, canine adenovairus type I, canine parvovirus, coronavirus and Leptospira spp.

Laboratory Methods

Blood samples were obtained through jugular venipuncture into vacuum tubes with EDTA (2 ml) (HemaandTube®, Turkey) as anticoagulant for hematological parameters and for lactate measurement and plain tubes (10 ml) (HemaandTube®, Turkey) for biochemical parameters. Hematological parameters, including total white blood cell count (WBC count) and differential, hematocrit rates (HCT), hemoglobin (Hgb), erythrocyte (RBC) and platelet counts, reticulocyte count were measured without time lag after sampling by an automatic analyzer (Cell-Dyne 3500®, Abott Inc., USA). Spherocytes were evaluated from blood smear of cases with IMHA. The presence of autoagglutination was determined by a slide agglutination test (1:1 dilution with isotonic saline solution). Blood for serum and plasma samples were centrifuged at 1000 xg for 20 minutes at 20ºC.

Albumin and total protein levels were measured by an auto analyzer (RA – XT®, Bayer Inc, Germany). Furthermore, the concentrations of urea, creatinine, bilirubine, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and Gamma-glutamyltransferase (GGT) were assessed by Reflotron® (BoehringerandMonnheim Inc., Germany).

Treatment

Dogs included in the present study were divided into 3 groups (15 dogs in each group) and three different therapy protocols were constituted into each group. Prednisolone (Prednisolon®, Fako Inc., Istanbul, Turkey; 2 mg/kg, i.m., Q12 h for 3 weeks) was administered in the group I. Danazol (Danazin ®, Kocak Inc., Istanbul, Turkey; 5 mg/kg, P.O., Q12 h for 3 weeks) was used in group II and testosterone

propionate (Sustanon–250, Organon Inc., Istanbul, Turkey; 2.2 mg/kg, i.m., 3 times per week for 3 weeks) was administrated in the group III.

Statistical Analysis

The data were expressed as mean ± SE in order to detect the significant differences of the differences of the parametrical values in all groups in different times, repeated measures ANOVA test and Tukey test were used. The Mann-Whitney test was used for the differences between the groups at a given time. The Dunn's multiple comparison test was used as the post-test. Instat Statistical Program v2.02 (SPSS Inc., Illinois, USA) was used for the statistical analyses. For all comparisons, probability values less than 0.05 were considered as statistically significant.

Results

On the basis of clinical examinations, all dogs in the present study had exercise intolerance, pale mucous membranes, tachycardia, tachypnea, mental depression and lethargy. 28 of 45 the dogs had icterus, 3 dogs had hemoglobinuria, 24 dogs had petechial and ecchymotic bleeding in the mucous membranes and 4 dogs had epistaxis. Pre-and post-treatment clinical parameters for all groups are presented in Table I.

Table I. Mean (±SE) clinical findings at 0h, 1.day, 1.week and 3.week.

Tablo II. 0 ve 1 gün, 1 ve 3. hafta klinik bulgular

Parameters	Group	0 h	3. day	1. week	3. week
T (°C)	Prednisolone	38.4 ± 0.6	38.7 ± 0.5	38.4 ± 0.4	38.5 ± 0.7
	Danazol	38.5 ± 0.4	38.4 ± 0.8	38.8 ± 0.6	38.6± 0.3
	Testosterone	38.3 ± 0.5	38.6 ± 0.7	39.1 ± 0.3	38.8± 0.4
P (min)	Prednisolone	140.2 ± 14.8 ^{Aab}	132.4 ± 13.1 ^{ab}	118.6 ± 8.8^{Ac}	112.2 ± 9.6 ^{Ad}
	Danazol	134.4 ± 13.1^{ABab}	138.3± 14.2^{ab}	119.2± 13.1^{ABc}	121± 16.2^{ABd}
	Testosterone	138.0 ± 16.3^{C}	136.6 ± 19.2	133.6 ± 23.5^{C}	134.8 ± 21.2^{C}
R (min)	Prednisolone	42 ± 3.3^{a}	36.0 ± 2.8^{bc}	32.8 ± 1.7^{bcd}	29.9 ± 2.1^{dc}
	Danazol	37.1 ± 3.5^{ab}	33.6 ± 4.3^{ba}	30.6 ± 3.5^{cbd}	28.8 ± 2.8^{dc}
	Testosterone	39.4 ± 5.6	38.4 ± 3.5	36.3±4.2	35.8± 2.5

P:pulsation;R:respiration;T:temperature
'a', 'b', 'c' and 'd' represents differences between the values involving different letters on the same row are found to be statistically significant.
'A', 'B' and 'C' are significant difference among Prednisolon, Danazol and Testosteron measurements at the same time.
P < 0.05

Table II. Mean(±SE) hematological findings at 0h, 1.day, 1.week and 3.week

Tablo II. 0. ve 1. gün ve 1 ve 2 haftalardaki hematolojik bulgular

Parameters	Group	Base line	3. day	1. week	3. week
WBC (x10^3/µl)	Prednisolone	21.3±0.6^{a}	25.1±0.6^{Ab}	29.2±0.5A^{cd}	31±0.6^{cd}
	Danazol	19.8±0.9	16.7±0.8^{BC}	17.1±0.9^{BC}	16.8±0.8^{BC}
	Testosterone	20.1±0.6	18.2±0.5^{CB}	17.3±0.5^{CB}	15.2±0.5^{CB}
Neutrophil (x 10^3/µl)	Prednisolone	12.2±1.3^{a}	18.5±0.8^{Ab}	24.7±1.0^{Acd}	26.1±0.8^{Adc}
	Danazol	12.6±1.6	10.8±1.5^{BC}	9.3±1.3^{BC}	10.2±1.2^{BC}
	Testosterone	13.7±1.7	13.2±1.5^{CB}	12.4±1.6^{CB}	10.6±1.5^{CB}
Lymphocyte (x 10^3/µl)	Prednisolone	8.3±1.3^{a}	6.2±1.1^{bac}	4.9±1.2^{cbd}	4.3±1.2^{dc}
	Danazol	6.1±1.7	5.1±1.5	6.8±1.3	6.1±1.2
	Testosterone	6.3±4.0	4.7±4.5	4.3±4.1	5.2±1.6
RBC (mm^3 x 10^6)	Prednisolone	2.3±0.2.6^{a}	3.1±195.8^{Ab}	4.4±192.3^{Ac}	6.2±280.1^{Ad}
	Danazol	2.6.0±0.6^{a}	3.2±151.5 ABb	3.9±178.4 ABc	4.9±229.2^{Bd}
	Testosterone	2.2±182.8	2.4±195.5^{C}	2.5±194.4^{C}	2.7±213.7^{C}
HCT (%)	Prednisolone	15.4±1.9^{a}	19.8±1.0^{a}	25.1±1.4^{Ac}	36.5±0.7^{Ad}
	Danazol	14.3±1.6^{a}	16.9±0.8^{a}	24.2±1.2^{ABc}	30.7±0.6^{Bd}
	Testosterone	16.2±1.7	17.3±0.5	19.1±1.0^{C}	20.4±1.1^{C}
Hgb (g/dl)	Prednisolone	5.0±0.3^{a}	6.9±0.3^{b}	8.2±0.5^{Abc}	12.3±0.2^{Ad}
	Danazol	4.8±0.2^{a}	6.2±0.2^{b}	8.3±0.4^{ABbc}	10.3±0.2^{ABd}
	Testosterone	5.4±0.2	5.7±0.2	5.9±0.3^{C}	6.3±0.3^{C}
MCV (fl)	Prednisolone	88.2±0.6^{a}	77.2±0.7^{ab}	76.9±0.6^{Aabc}	70.8±0.8^{Ad}
	Danazol	83.2±0.6^{a}	78.6±0.8^{abc}	76.1±0.8^{Abc}	75.4±1.0^{ABd}
	Testosterone	86.9±0.6^{a}	82.3±0.7^{ab}	83.6±1.0^{Aabc}	80.2±1.3^{Cbcd}
MCHC (g/dl)	Prednisolone	37.6±0.3	34.3±0.3	33.3±0.3^{A}	34.8±0.2
	Danazol	36.2±0.3	35.5±0.3	34.5±0.3^{AB}	33.5±0.3
	Testosterone	37.1±0.5	36.5±0.5	36.0±0.5^{BC}	35.7±0.5
PLT (mm^3 x 10^3)	Prednisolone	62.2±7.1^{a}	98.733±8.3^{Ab}	175.9±13.4^{Ac}	329.2±20.5^{Ad}
	Danazol	70±9.8^{a}	125±10.8^{Bb}	226.1±11.0^{Bc}	343.3±18.4^{ABd}
	Testosterone	68±5.3	63±4.5^{C}	69.3±3.8^{C}	92±3.5^{C}

WBC:white blood cell;RBC:erythrocyte;Hgb:haemoglobin;HCT:hematocrit ;MCV:mean corpuscular volume;MCHC:mean coropusculer haemoglobin concentration; PLT: thrombocyte
'a', 'b', 'c' and 'd' represents differences between the values involving different letters on the same row are found to be statistically significant.
'A', 'B' and 'C' are significant difference among Prednisolon, Danazol and Testosteron measurements at the same time.
P < 0.05

Table III. Mean(±SE) serum biochemical findings at 0h, 1.day, 1.week and 3.week

Tablo III. 0. ve 1. gün ve 1 ve 2 haftalardaki serum biyokimyasal bulgular

Parameters	Group	0 h	3. day	1. week	3. week
Albumin (g/dl)	Prednisolone	3.1±0.07	2.9±0.07	3.2±0.05	3.5±0.07
	Danazol	3.4±0.06	3.1±0.05	2.9±0.05	3.2±0.06
	Testosterone	3.2±0.06	3.5±0.07	3.3±0.05	3.1±0.04
ALT (U/L)	Prednisolone	84.2±4.3^{Aa}	90.7±5.5^{Ab}	107.4±6.7^{Ac}	133.0±5.6^{Ad}
	Danazol	113.4±6.2^{Ba}	93.4±5.1^{ABb}	81.2±4.4^{Bbc}	55.4±4.6^{Bd}
	Testosterone	128.3±6.7^{BCa}	113.7±7.9^{Cab}	98.6±8.9^{ACc}	86.4±9.4^{Cdc}
GGT (U/L)	Prednisolone	14.7±0.07	19.3±0.08	20.2±0.09	21.2±0.09
	Danazol	16.1±0.09	17.2±0.1	16.3±0.08	15.3±0.06
	Testosterone	15.9±0.06	14.1±0.07	17.3±0.06	16.0±0.04
AST (U/L)	Prednisolone	40.8±1.4^{a}	63.7±2.8^{Aab}	81.6±2.7^{Acb}	117.6±3.9^{Ad}
	Danazol	39.8±3.3^{a}	58.4±3.7^{ABb}	70.0±3.8^{ABc}	84.5±2.5^{Bd}
	Testosterone	39.8±3.3^{a}	42.5±1.9^{CB}	53.0±1.9^{cC}	67.5±2.1^{dC}
Bilirubin (mg/dl)	Prednisolone	1..9±0.2^{a}	1.6±0.4^{ab}	1.1±0.1^{c}	0.3±0.03^{Ad}
	Danazol	2.1±0.1^{a}	1.4±0.4^{bc}	1.3±0.1^{cb}	0.4±0.07^{ABd}
	Testosterone	1.7±0.1	1..8±0.5	1.7±0.1	1.4±0.1^{C}
Urea (mg/dl)	Prednisolone	28.5 ± 8.5	31.8 ± 8.4	30.5 ± 9.0	27 ± 10.0
	Danazol	26.5 ± 7.3	28.3±6.2	29±6.5	28..3±4.6
	Testosterone	31.2±6.5	27.2±7.3	26.7±6.1	29.8±5.3
Creatinine (mg/dL)	Prednisolone	1.4±2.3	1.3±2.6	1.6±3.0	1.7±4.1
	Danazol	1.3±3.1	1.6±4.2	1.8±5.4	1.6±5.3
	Testosterone	1.5±3.2	1.8±3.2	1.9±4.3	1.9±3.4

ALT:*alanine* aminotransferase;AST:aspartate aminotransferase;GGT:*Gamma*-glutamyl transpeptidase
'a', 'b', 'c' and 'd' represents differences between the values involving different letters on the same row are found to be statistically significant.
'A', 'B' and 'C' are significant difference among Prednisolon, Danazol and Testosteron measurements at the same time.
P < 0.05

At presentation, all dogs had hematocrit values less than 30 %. Hemoglobin and hematocrit levels were significantly higher in group I and II compared with group III at the end of treatment (P=0.05). In group III, many of cases did not reach into reference values at the end of therapy (Table II).

In admission, all dogs had macrocytic anemia. All dogs were thrombocytopenic (<100.000/μL). Although, thrombocyte values reached to reference limits in group I and II at the end of the therapy, it was lower than the reference limits in group III. In all dogs, the mean corrected reticulocyte count was 4.4%, Spherocytosis and auto agglutination were detected in 45 of 45 (100%). Pre–treatment, all dogs had high total leukocyte values (>17,000 leukocytes/μL). Group I had slightly higher total leukocyte values, compared with other groups

Serum ALT activity were significantly increased at base line, third day, first week and third week in group I when compared to group II and III (P<0.05). AST concentration significantly increased in all groups at the end of treatment. ALT and AST concentration in Group I were higher than group II and group III (P<0.05). There were no significant differences in GGT, serum BUN and creatinine concentrations after treatment in all groups. Bilirubin concentration significantly decreased in group I at all times (p<0.05). (Table III)

Addition to the treatment protocol in the study, thirty-three dogs (73.3%) received whole blood transfusions because of severe anemia. Classical treatment (Prednisolon®, Fako Inc., Istanbul, Turkey; 2 mg/kg, i.m., Q12 h) were applied for cases that were not resoponded to treatment at the end of the treatment period in group II and group III. The average PCV before the transfusion was 14.6±0.3% with a range of 12-15 %, and average PCV after the transfusion was 22.6±0.4%, with a range of 19-26%. Clinically significant adverse reactions were not observed regarding with blood transfusion.

Discussion

Ages of dogs (mean 4.5 years) with IMHA consisted to present study was similar to those reported in previous studies[7,16,18,32]. In the previous studies, it was shown[16,25] that intact female dogs with IMHA are overrepresented. However, we couldn't compare the neutered and intact males/females because all dogs included to the study were neutered. In our study there were no significant difference between male and females. Although Cocker spaniel dogs were most common reported breed in previous studies[16-18,32] Terrier and Labrador retriever breeds were overrepresented in the present study.

Leukocytosis in dogs with IMHA may occur as a result of combination of different cause such as myeloid hyperplasia due to cytokines, demargination of neutrophils[3]. In a previous study[23] reported that tissue necrosis associated with anemic hypoxia and thromboembolic disease should be considered when leukocytoses are observed in dogs with IMHA. In present study, it was found that total leukocyte value were high than reference limit in all groups. In group I, total leukocyte were higher than other groups. Although we could not go into details for thromboembolic disease, we thought that leukocytosis might be occurred fallowing prednisolone application in group I or it may be related with above mentioned[3].

In previous studies[13,34] high serum ALT and GGT values were reported in dogs treated with Prednisolone. Similarly in the present study, ALT and GGT levels were increased throughout the treatment group I although other groups were normal during therapy. In human, the long-term use of androgen may be associated with an increased, though quite small, risk of certain types of liver disease[9,14,19]. Various studies reported hepatic damage induced by treatment with Danazol[20,39]. Cicardi et al., (1983)[8] reported that long-term treatment (15 to 47 mo) with low doses of danazol or stanozolol were not induce significant hepatic damage detectable by laboratory tests or liver biopsy. These possible adverse effects, described in humans are, to our knowledge, not yet described in dogs. In our study, although danazole and testosterone propionate were used, we were not observed any adverse effect. There were also no influence on liver enzyme activities and other serum biochemical parameters.

Various of immunosuppressive protocols are used in the management of IMHA in veterinary medicine. One of the drug classes is the glucocorticoids which is the functioned to inhibit Fc-receptor mediated clearance of Ig G sensitized erythrocytes in the spleen, and may inhibit autoantibody synthesis. The use of corticosteroids to reduce the degree of phagocytosis and antibody production is reasonable and well accepted[2,11]. In previous studies reported[4,15,16,21] that immunesuppresive doses of prednisolone is

effective in patients with IMHA. In present study, Prednisolone in group I which was administrated, it was detected that hematologic values, except total leuckocyte values, reached to reference interval at the end of the therapy period[4,15,16,21].

There is little agreement on how to treat AIHA when corticosteroid therapy fails is ineffective or is not an option[30]. Treatments for these patients include low-dose cytotoxic therapy[30,33], danazol (c) and intravenous immunoglobulin[10]. Otherwise, anabolic steroids such as androgens have various indications[31] of which the most well known are inducing erythropoiesis and treatment of metastasised mammary carcinomas in females[14]. However, there are also studies describing their use in immune-mediated disorders. In humans studies, Danazol, a synthetic androgen, appeared to be effective in human patients[1] with immune-mediated hemolytic anemia and thrombocytopenia. Bloom et al., (1989)[6] and Holloway et al., (1990)[15] reported that they used it successfully in immune-mediated thrombocytopenia in dogs. In the present study, *we found that danazol is* useful in the treatment of immune mediated anemia and thrombocytopenia in dogs. However, to our knowledge, there are no published controlled studies in a larger series of dogs. Further studies are needed to completely understand effect on immune mediated hemolytic anemia and thrombocytopenia.

In humans, androgen treatment inhibits B cell hyperactivity and immunoglobulin production by mononucleated cells in patients with Systemic Lupus Erythematosus[27] and decreases CD4+ cells in post-menopausal women[41]. These observations are supported by clinical data, which suggest a role for androgens in the immune modulation of autoimmune diseases[5,29,37]. Long-term administration of androgenic preparations has been reported to increase red cell volume[30,27]. Yeo et al., (2000)[40] suggested that testosterone propionate may be effective in prevention of immune mediated sensorineural hearing loss in rat. However, in the present study, we found that danazol treatment were more effective compared with testosterone propionate treatment. Testosterone propionate have no effect on treatment of IMHA, however, we thought that it may be related to short using period of testosterone propionate or short observing period after treatment.

In conclusion in this study, despite the normal response to conventional treatment, prednisolone therapy and danazol as synthetic androgen, it was deterimined that there were no anticipated effects by testosterone propionate for treatment of AIHA in dogs. Further studies on a larger population with long-term follow-up and monitoring of the blood parameters are required to better evaluate its usefulness and safety compared with other therapeutic drugs.

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