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Research Article

EFFECT OF DOXORUBICIN ON HAEMATOLOGICAL AND BLOOD BIOCHEMICAL PROFILE OF HEALTHY DOGS

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ABSTRACT

The study was conducted in 10 clinically healthy adult dogs to evaluate the effect of doxorubicin on haematological and blood biochemical parameters. The drug was administered twice @ 1.0 mg/kg intravenously to all the dogs at an interval of three weeks in first group and two weeks in second group. Blood sampling was done before administration of doxorubicin and on 5th, 10th, 20th, 26th, 31st and 41st day of drug administration in group I and on 5th,10th, 19th and 24thday of drug administration in group II. There was a significant fall in the TEC, TLC, neutrophils, eosinophils and thrombocytes indicating bone marrow suppression. The ALT, AST, ALP, GGT, urea, BUN, creatinine, and LDH were increased indicating damage to gastro intestinal tract, hepatotoxicity andcardiotoxicity. On the basis of clinical observation, haematological study and blood biochemical study, doxorubicin hydrochloride seems to be gastrotoxic, hepatotoxic and cardiotoxic.

Key words: Cardiotoxicity, Dogs, Doxorubicin hydrochloride, Hepatotoxicity

Many a times dogs suffer from diseases such as transmissible venereal tumour (TVT) and tumours like haemangiosarcoma, lymphosarcoma, mast cell tumors, brain tumors, osteosarcoma, thyroid cancer, melanoma and mammary neoplasm. These animals undergo chemotherapy, radiation therapy and surgeries as therapeutic measures. The animal undergoing chemotherapy experiences various adverse effects of these agents like myelosuppression, GIT disturbances such as vomiting, diarrhoea, dysphagia, decreased appetite, weight loss, immunosuppression, cardiotoxicity, hypersensitivity, alopecia and extravasation injury. Doxorubicin is one of the potent and often used chemotherapeutic agents in veterinary and human oncology. In order to establish a better chemotherapeutic regime and to reduce the toxic effects of the drug, it is necessary to understand these adverse effects in details.

MATERIALS AND METHODS

The study was conducted on 10 clinically healthy adult mongrel dogs divided into two groups of five animals each weighing between 12-20 kg irrespective of the age, breed and sex to evaluate the effect of doxorubicin hydrochloride on haematological and blood biochemical parameters.

Group I: Doxorubicin was administered at the dose rate of 1.0 mg/kg intravenously twice at an interval of three weeks. Blood sampling was done before administration of doxorubicin hydrochloride and on5th, 10th, 20th, 26th, 31stand 41st day of drug administration.

Group II: Doxorubicin was administeredat the dose rate of 1.0 mg/kg intravenously twice with an interval of two weeks. Blood sampling was done before administration of doxorubicin hydrochloride and on 5th, 10th, 19th and 24th day of drug administration.

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All the dogs were monitored continuously for various adverse effects like nasal discharge, restlessness, inappetance, anorexia, vomiting and diarrhoea. Blood samples were collected in EDTA vials for haematology and in 3.8% sodium fluoride vials for glucose estimation and vials without any anticoagulant for the collection of the serum. Haematological estimation was conducted immediately after the blood collection with haematology cell counter (Haematology Cell Counter MS4s, France). Samples for serum and plasma separation were kept for one hour and then centrifuged at 3000rpm for 10 minutes to separate plasma and serum. The separated samples were stored at -20°C until the estimation. Various biochemical parameters were estimated using semi automatic clinical chemistry (Agappe Diagnostics Lim, India) analyzer with ready to use kits from Transasia Ltd. (Transasia Bio Medicals Ltd, India).

To evaluate the effect of doxorubicin on various systems, following parameters were estimated at various intervals as mentioned above: haemoglobin (Hb), packed cell volume (PCV), total erythrocyte count (TEC), total leukocyte count (TLC), differential leukocyte count (DLC) and total platelet count (thrombocytes), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), glucose, triglycerides, total cholesterol, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), direct bilirubin, urea, blood urea nitrogen (BUN), creatinine, total plasma proteins, albumin, globulin, albumin:globulin ratio (A:G ratio), sodium, potassium, chloride, calcium and cortisol. Statistical analysis of the data was done by one way ANOVA using Duncan multiple range test.

RESULTS AND DISCUSSION

All the dogs exhibited nasal discharge during administration of the drug, one dog showed restlessness for a short period of one minute during administration of first dose in both the groups, which might be due to rapid infusion of drug or indication of anaphylaxis.

In group I- four dogs were in-appetent after first dose and three after second dose, one dog was completely anorectic after second dose. Four dogs suffered from diarrhoea out of which two had bloody diarrhoea after first dose and three dogs had diarrhoea after second dose. In group II, three dogs were in-appetent, one dog was anorectic and three dogs suffered from diarrhoea after both the administration of the drug. These clinical signs noticed might be due to damage to GIT mucosa and liver caused by the doxorubicin. Yadav (2014) reported that dogs suffering from TVT treated with doxorubicin also showed vomiting and diarrhoea in 4 out of 8 dogs and 2 out of 8 dogs, respectively. During the administration of doxorubicin, the occurrence of anxiety, face oedema, trembling of the head could be a sign for a too rapid infusion or indication of anaphylaxis (Todorova *et al.*, 2005). Chemotherapy kills rapidly dividing cells; unfortunately chemotherapeutic drugs do not differentiate between tumor cells and normal cells. In general side effects of chemotherapy include bone marrow suppression, gastrointestinal problems like nausea, vomiting, diarrhoea and alopecia. Vomiting, anorexia and diarrhoea are due to damage of the gastrointestinal epithelium or CNS effects (Chun *et al.*, 2007).

Table 1
Various clinical sig]ns observed during the study

Clinical observations	Total no. of dogs	No. of animals affected			
		After first dose of doxorubicin		After second dose of doxorubicin	
		Group I	Group II	Group I	Group II
Nasal discharge	10	05	05	05	05
Anxiety	10	01	01	00	00
Inappetence	10	04	03	03	03
Anorexia	10	00	01	01	01
Vomiting	10	00	00	00	00
Diarrhoea	10	04	03	03	03
Bloody diarrhoea	10	02	00	00	00

In both the groups, there was a significant decrease in total leucocyte count, total erythrocyte count and packed cell volume (Table 2 & 3).

The decrease in above parameters might be due to the bone marrow suppression by doxorubicin. Bone marrow cells divide very rapidly because of their high growth fraction (Mac Donald, 2009) and activity of most anticancerous drugs is greatest in tissues with a high growth fraction; however, anaemia is rare and usually only mild to moderate. Similar findings were recorded by Yadav (2014) and Phogat (2015) in dogs undergoing chemotherapy for TVT with doxorubicin. A non-

Table 2
Effect of doxorubicin on haematological parameters at different intervals in five dogs of group I (Mean ± S.E.)

Parameters	0 day, 1st dose	5th day	10th day	20th day, 2nd dose at 21st day	26th day	31st day	41st day
Hb (g/dL)	11.80^{a} ± 0.58	11.44^{a} ± 0.68	11.24^{a} ± 0.4	10.98^{a} ± 0.32	11.84^{a} ± 0.31	12.10^{a} ± 0.49	10.86^{a} ± 0.53
TLC (x10³/mm³)	12.12^{a} ± 1.7	10.66^{a} ± 1.82	9.27^{a} ± 2.32	11.19^{a} ± 1.77	11.95^{a} ± 3.36	7.24^{a} ± 1.41	11.16^{a} ± 1.49
TEC (x106/mm³)	6.30^{a} ± 0.46	6.24^{a} ± 0.29	6.54^{a} ± 0.18	6.95^{a} ± 0.66	6.62^{a} ± 0.18	6.29^{a} ± 0.24	6.41^{a} ± 0.29
PCV (%)	36.68^{a} ± 0.79	36.86^{a} ± 1.45	37.0^{a} ± 1.07	42.64^{a} ± 3.69	40.52^{a} ± 1.23	40.54^{a} ± 2.29	40.42^{a} ± 1.56
Neutrophils (%)	54.00^{ab} ± 4.09	54.00^{ab} ± 4.14	58.00^{ab} ± 4.62	56.60^{ab} ± 7.83	43.80^{b} ± 4.73	63.00^{a} ± 3.49	54.20^{ab} ± 5.54
Basophils (%)	0.40^{a} ± 0.25	0.80^{a} ± 0.2	0.60^{a} ± 0.25	0.60^{a} ± 0.25	0.80^{a} ± 0.20	1.20^{a} ± 0.20	0.80^{a} ± 0.37
Eosinophil (%)	3.80^{a} ± 0.55	1.60^{ab} ± 0.68	0.60^{b} ± 0.25	2.20^{ab} ± 0.74	1.60^{ab} ± 0.68	2.00^{ab} ± 0.32	3.60^{ab} ± 2.14
Lymphocytes (%)	36.80^{ab} ± 4.33	36.40^{ab} ± 3.95	33.40^{b} ± 4.01	33.60^{b} ± 7.16	49.00^{a} ± 5.18	29.27^{ab} ± 3.22	42.40^{ab} ± 4.32
Monocytes (%)	5.00^{bc} ± 0.45	7.00^{ab} ± 0.84	7.60^{a} ± 0.68	7.00^{ab} ± 0.05	5.00^{bc} ± 0.32	4.60^{c} ± 0.4	4.60^{c} ± 0.57
Thrombocytes (x10³/mm³)	346.60^{a} ± 81.82	317.60^{a} ± 49.74	288.40^{a} ± 67.69	225.40^{a} ± 56.07	217.40^{a} ± 43.12	242.80^{a} ± 48.58	346.00^{a} ± 35.98
MCV (fl)	60.98^{a} ± 1.85	61.82^{a} ± 0.59	61.00^{a} ± 2.10	60.64^{a} ± 2.19	61.34^{a} ± 1.92	63.98^{a} ± 2.75	62.50^{a} ± 2.07
MCH (pg)	18.02^{a} ± 0.63	17.48^{a} ± 0.42	17.14^{a} ± 0.6	17.20^{a} ± 1.07	17.56^{a} ± 0.64	18.26^{a} ± 0.59	18.14^{a} ± 0.47
MCHC (g/dL)	29.50^{a} ± 0.44	28.90^{a} ± 0.36	26.00^{a} ± 2.08	26.12^{a} ± 1.28	28.68^{a} ± 0.30	28.06^{a} ± 0.84	28.88^{a} ± 1.01

Means with different superscripts vary significantly ($p<0.05$)

Table 3
Effect of doxorubicin on haematological parameters at different intervals in five dogs of group II (Mean ± S.E.)

Parameters	0 day, 1st dose	5th day	10th day, 2nd dose at 14th day	19th day	24th day
Hb (g/dL)	$11.64^{a}\pm0.27$	$10.34^{a}\pm0.29$	$10.68^{a}\pm0.55$	$10.68^{a}\pm0.42$	$11.52^{a}\pm0.52$
TLC (x10³/mm³)	$11.23^{a}\pm1.26$	$7.44^{b}\pm0.97$	$7.34^{b}\pm1.08$	$5.85^{b}\pm0.99$	$7.24^{b}\pm1.56$
TEC (x106/mm³)	$6.25^{a}\pm0.24$	$5.49^{ab}\pm0.26$	$6.10^{ab}\pm0.18$	$5.35^{b}\pm0.32$	$5.88^{ab}\pm0.34$
PCV (%)	$39.56^{ab}\pm1.35$	$35.98^{bc}\pm1.81$	$36.26^{bc}\pm1.75$	$33.28^{c}\pm1.67$	$41.56^{a}\pm1.52$
Neutrophils (%)	$59.20^{a}\pm2.18$	$63.60^{a}\pm1.63$	$57.60^{a}\pm8.49$	$64.00^{a}\pm9.61$	$63.40^{a}\pm7.45$
Basophils (%)	$0.60^{ab}\pm0.25$	$0.80^{ab}\pm0.20$	$0.20^{b}\pm0.20$	$0.40^{ab}\pm0.25$	$1.00^{a}\pm0.0$
Eosinophils (%)	$1.40^{ab}\pm0.4$	$2.00^{a}\pm0.32$	$0.80^{b}\pm0.20$	$1.40^{ab}\pm0.25$	$2.00^{a}\pm0.45$
Lymphocytes (%)	$36.20^{a}\pm1.93$	$29.20^{ab}\pm1.56$	$28.20^{ab}\pm2.65$	$20.60^{b}\pm3.36$	$23.40^{b}\pm3.96$
Monocytes (%)	$4.60^{ab}\pm0.25$	$4.40^{b}\pm0.50$	$4.40^{b}\pm0.40$	$6.40^{a}\pm0.93$	$6.20^{ab}\pm0.74$
Thrombocytes (x10³/mm³)	$347.80^{a}\pm31.18$	$308.80^{a}\pm32.16$	$304.60^{a}\pm55.10$	$365.20^{a}\pm65.79$	$295.40^{a}\pm44.45$
MCV (fl)	$59.50^{a}\pm1.63$	$59.84^{a}\pm0.92$	$60.42^{a}\pm1.09$	$59.30^{a}\pm1.92$	$60.04^{a}\pm1.38$
MCH (pg)	$18.98^{a}\pm1.47$	$16.88^{a}\pm0.70$	$17.42^{a}\pm0.65$	$20.18^{a}\pm1.72$	$17.32^{a}\pm0.49$
MCHC (g/dL)	$30.36^{ab}\pm1.47$	$28.56^{a}\pm0.24$	$29.16^{a}\pm0.88$	$32.82^{b}\pm1.97$	$29.04^{a}\pm0.38$

Means with different superscripts vary significantly ($p<0.05$)

significant increase in MCV was noticed in both the groups; a non-significant decrease in MCHC in group I and significant increase in group II was noticed. Macrocytosis (increase in MCV) correlates with the regenerative anaemia (Marks, 2016).

In both the groups, there was a significant decrease in the total plasma proteins, albumin and globulin, whereas there was a non-significant increase in ALT and AST whereas a significant increase in ALP and GGT this might be due to hepatotoxicity of drug (Behera *et al.*, 2012). There was a significant increase in CK and LDH (Table 4 & 5).

This increase in above parameters might be due to the cardiotoxic effect of doxorubicin. The reported incidence of cardiotoxicity in doxorubicin treated dogs is varying between 8-64% depending on the chemotherapy protocol used and the criteria for diagnosis of toxicity (Sorenmo *et al.*, 2004; Gillings *et al.*, 2009; Ratterree *et al.*, 2012). Cardiotoxicity is of two types, type 1 (irreversible) or type 2 (reversible) based on the effect of chemotherapeutic agent on cardiomyocytes (Ewer and Ewer, 2008). The long-term cardiotoxicity caused by anthracyclines includes cardiomyocyte death and therefore it represents a

Table 4
Effect of doxorubicin on blood biochemical parameters at different intervals in five dogs of group I (Mean±standard error)

Parameters	0 day, 1st dose	5th day	10th day	20th day, 2nd dose at 21st day	26th day	0 day, 1st dose	5th day
Total Plasma Proteins (g/dL)	$6.67^{a}\pm0.21$	$6.44^{a}\pm0.17$	$6.45^{a}\pm0.15$	$6.65^{a}\pm0.27$	$6.49^{a}\pm0.21$	$5.94^{a}\pm0.35$	$6.59^{a}\pm0.31$
Albumin (g/dL)	$3.75^{a}\pm0.17$	$3.36^{ab}\pm0.06$	$3.31^{b}\pm0.29$	$3.13^{b}\pm0.24$	$3.17^{b}\pm0.07$	$3.29^{b}\pm0.11$	$3.24^{b}\pm0.29$
Globulin(g/dL)	$2.93^{a}\pm0.36$	$3.07^{a}\pm0.12$	$3.03^{a}\pm0.18$	$3.52^{a}\pm0.82$	$3.31^{a}\pm0.24$	$2.67^{a}\pm0.34$	$3.35^{a}\pm0.34$
A:G ratio	$1.40^{a}\pm0.24$	$1.10^{ab}\pm0.06$	$1.11^{ab}\pm0.1$	$1.91^{b}\pm0.11$	$0.98^{ab}\pm0.07$	$1.32^{ab}\pm0.18$	$1.02^{ab}\pm0.15$
ALT (IU/L)	$23.73^{a}\pm2.0$	$26.90^{a}\pm2.20$	$25.88^{a}\pm1.83$	$27.99^{a}\pm7.58$	$36.94^{a}\pm1.38$	$37.07^{a}\pm1.22$	$28.54^{a}\pm5.26$
AST (IU/L)	$25.97^{a}\pm2.86$	$26.13^{a}\pm3.98$	$22.44^{a}\pm2.85$	$29.67^{a}\pm7.17$	$22.57^{a}\pm4.17$	$19.78^{a}\pm3.57$	$27.40^{a}\pm4.59$
ALP (IU/L)	$105.67^{ab}\pm4.66$	$111.06^{a}\pm2.36$	$95.56^{bc}\pm5.6$	$92.23^{cd}\pm3.37$	$84.91^{cd}\pm3.9$	$79.76^{d}\pm3.78$	$86.19^{cd}\pm6.02$
GGT (IU/L)	$9.43^{ab}\pm0.50$	$7.16^{b}\pm0.52$	$11.71^{ab}\pm3.75$	$14.91^{a}\pm4.51$	$6.20^{b}\pm1.09$	$6.85^{b}\pm0.66$	$8.27^{ab}\pm0.52$
CK (IU/L)	$81.97^{b}\pm1.20$	$225.64^{b}\pm4.93$	$192.8^{b}\pm2.31$	$185.64^{b}\pm1.22$	$341.28^{ab}\pm6.98$	$365.42^{ab}\pm9.39$	$589.54^{a}\pm2.03$
LDH (IU/L)	$237.70^{a}\pm4.58$	$482.02^{a}\pm2.03$	$180.45^{a}\pm7.98$	$164.88^{a}\pm2.93$	$131.92^{a}\pm4.71$	$296.60^{a}\pm7.81$	$360.9^{a}\pm1.67$
Bilirubin (mg/dL)	$0.27^{b}\pm0.08$	$0.39^{ab}\pm0.08$	$0.37^{b}\pm.10$	$0.59^{b}\pm0.12$	$0.75^{a}\pm0.11$	$0.47^{ab}\pm0.12$	$0.35^{b}\pm0.16$
Urea(mg/dL)	$34.11^{bc}\pm1.19$	$31.77^{c}\pm3.73$	$26.72^{c}\pm3.88$	$34.12^{bc}\pm4.72$	$59.77^{a}\pm7.52$	$48.95^{ab}\pm7.16$	$37.24^{bc}\pm5.39$
BUN(mg/dL)	$15.94^{bc}\pm0.56$	$14.84^{c}\pm1.74$	$12.48^{c}\pm1.81$	$15.94^{bc}\pm2.2$	$27.93^{a}\pm3.57$	$22.87^{ab}\pm3.34$	$17.40^{bc}\pm2.52$
Creatinine(mg/dL)	$1.33^{a}\pm0.17$	$1.11^{a}\pm0.05$	$1.15^{a}\pm0.004$	$1.12^{a}\pm0.09$	$1.17^{a}\pm0.02$	$1.21^{a}\pm0.04$	$1.16^{a}\pm0.07$
Cholesterol(mg/dL)	$243.74^{a}\pm1.94$	$216.98^{ab}\pm2.54$	$175.72^{b}\pm5.12$	$194.32^{ab}\pm1.27$	$207.10^{ab}\pm1.37$	$205.48^{ab}\pm9.42$	$211.52^{ab}\pm1.44$
Triglycerides(mg/dL)	$51.37^{a}\pm1.25$	$70.74^{a}\pm1.28$	$75.45^{a}\pm1.19$	$73.21^{a}\pm8.12$	$71.19^{a}\pm7.56$	$63.76^{a}\pm1.24$	$62.79^{a}\pm1.54$
Glucose(mg/dL)	$125.48^{a}\pm6.80$	$131.84^{a}\pm1.03$	$131.14^{a}\pm3.99$	$129.52^{a}\pm3.36$	$125.24^{a}\pm3.85$	$120.78^{a}\pm1.79$	$127.28^{a}\pm1.51$
Cortisol(µg/dL)	$1.57^{a}\pm0.08$	$1.92^{a}\pm0.19$	$1.92^{a}\pm0.06$	$1.85^{a}\pm0.103$	$1.59^{a}\pm0.16$	$1.76^{a}\pm0.07$	$1.69^{a}\pm0.10$
Sodium(mmol/L)	$140.30^{c}\pm1.66$	$141.30^{bc}\pm1.12$	$145.22^{ab}\pm0.71$	$143.92^{abc}\pm1.36$	$145.92^{a}\pm1.02$	$143.32^{abc}\pm1.71$	$146.28^{a}\pm1.57$
Potassium(mmol/L)	$4.86^{a}\pm0.21$	$4.82^{a}\pm0.19$	$4.75^{a}\pm0.19$	$4.61^{a}\pm0.12$	$4.44^{a}\pm0.18$	$4.66^{a}\pm0.16$	$4.67^{a}\pm0.16$
Chloride(mmol/L)	$122.6^{ab}\pm0.76$	$118.4^{c}\pm0.19$	$119.48^{bc}\pm0.69$	$119.90^{abc}\pm1.36$	$123.66^{a}\pm1.45$	$121.16^{abc}\pm1.98$	$120.62^{abc}\pm1.22$
Calcium(mmol/L)	$10.90^{a}\pm0.58$	$11.34^{a}\pm0.22$	$10.29^{a}\pm0.26$	$10.84^{a}\pm0.43$	$10.54^{a}\pm0.49$	$11.79^{a}\pm0.55$	$11.27^{a}\pm0.62$

Means with different superscripts vary significantly ($p<0.05$)

Table 5
Effect of doxorubicin on blood biochemical parameters at different intervals in five dogs of group II (Mean ± S.E.)

Parameters	0 day, 1st dose	5th day	10th day, 2nd dose at 14th day	19th day	24th day
Total Plasma Proteins (g/dL)	6.82^{a}±0.10	5.92^{b}±0.26	6.01^{b}±0.32	5.37^{b}±0.23	6.07^{b}±0.28
Albumin (g/dL)	3.45^{ab}±0.15	3.34^{ab}±0.14	3.21^{b}±0.05	3.61^{a}±0.06	3.28^{b}±0.04
Globulin (g/dL)	3.36^{a}±0.10	2.58^{ab}±0.24	2.80^{ab}±0.78	2.16^{b}±0.11	2.79^{ab}±0.28
A:G ratio	1.05^{a}±0.11	1.37^{a}±0.12	1.24^{a}±0.2	1.49^{a}±0.12	1.27^{a}±0.06
ALT (IU/L)	22.20^{ab}±1.01	23.90^{ab}±1.21	22.81^{ab}±3.82	20.59^{b}±1.89	27.21^{a}±8.91
AST (IU/L)	20.67^{a}±1.60	21.75^{a}±3.39	23.66^{a}±3.76	28.35^{a}±3.18	25.36^{a}±3.16
ALP (IU/L)	74.81^{b}±7.12	98.10^{ab}±3.03	91.98^{ab}±1.06	82.76^{ab}±7.39	104.07^{a}±9.26
GGT (IU/L)	5.76^{b}±0.35	6.54^{b}±0.47	7.89^{b}±0.85	6.63^{b}±0.83	11.11^{a}±0.74
CK (IU/L)	93.19^{b}±2.24	153.78^{b}±3.68	329.80^{a}±4.83	281.74^{a}±9.38	319.04^{a}±4.14
LDH (IU/L)	221.90^{b}±2.30	293.81^{ab}±4.02	250.76^{ab}±4.89	489.10^{a}±1.29	352.96^{ab}±1.01
Bilirubin (mg/dL)	0.27^{a}±0.05	0.37^{a}±0.13	0.35^{a}±0.11	0.18^{a}±0.00	0.21^{a}±0.02
Urea (mg/dL)	32.40^{a}±7.12	30.80^{a}±3.41	32.92^{a}±5.24	43.97^{a}±3.76	32.65^{a}±6.57
BUN (mg/dL)	14.88^{b}±0.21	14.39^{b}±1.59	15.40^{b}±2.44	22.59^{a}±1.44	15.26^{b}±3.07
Creatinine (mg/dL)	0.87^{c}±0.04	1.17^{ab}±0.09	1.11^{bc}±0.11	1.44^{a}±0.54	1.29^{ab}±0.26
Cholesterol (mg/dL)	193.40^{ab}±6.57	193.88^{ab}±4.57	185.8^{b}±9.29	192.0^{ab}±4.41	222.0^{a}±2.13
Triglycerides (mg/dL)	45.73^{a}±9.34	68.61^{a}±1.33	73.39^{a}±2.04	46.18^{a}±1.34	7.24^{a}±1.13
Glucose (mg/dL)	116.06^{a}±4.25	123.40^{a}±0.61	129.50^{a}±0.98	116.40^{a}±2.69	134.94^{a}±1.63
Cortisol (mg/dL)	1.52^{a}±0.10	1.68^{a}±0.09	1.78^{a}±0.16	1.57^{a}±0.15	1.69^{a}±0.10
Sodium (mmol/L)	143.86^{b}±1.15	143.22^{b}±1.02	143.82^{b}±1.03	148.86^{a}±1.39	143.82^{b}±1.12
Potassium (mmol/L)	4.26^{b}±0.04	4.52^{ab}±0.12	4.62^{a}±0.15	4.36^{ab}±0.66	4.47^{ab}±0.06
Chloride (mmol/L)	122.54^{a}±0.17	119.98^{ab}±0.34	119.38^{b}±0.43	121.94^{ab}±0.72	120.02^{ab}±1.51
Calcium (mmol/L)	11.16^{a}±0.37	10.24^{a}±0.93	11.30^{a}±0.41	11.29^{a}±0.57	11.65^{a}±0.31

Means with different superscripts vary significantly ($p<0.05$)

type I cardiotoxicity (Volkova and Russell, 2011). In the normal dogs, CK-MB reference range is 4.9- 6.3IU/L (Montes *et al.*, 1987). In two dogs after two days of trauma, the serum activity of creatine kinase-muscle/brainwas 3882 IU/L and 8030 IU/L in two dogs, respectively suggesting an extensive myocardial injury (Diniz *et al.*, 2007). There was a significant increase in bilirubin, urea, BUN, creatinine, sodium, potassium and a significant decrease in chlorides which could be due to cytotoxicity caused by the drug (Gadmade, 2006). On the bases of clinical observations, haematological and blood biochemical study, doxorubicin hydrochloride seems to be gastro-toxic, hepatotoxic and cardio-toxic.

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