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Research Article

EFFECT OF VINCRISTINE SULPHATE ON HAEMATO-BIOCHEMICAL PROFILE OF HEALTHY DOGS

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ABSTRACT

The study was conducted on 10 clinically healthy adult dogs divided into two groups (group I and group II) of five each, to evaluate the effect of vincristine sulphate on haematological and blood biochemical parameters. Vincristine sulpahte was administered once a week for three weeks to all the dogs of group I @ 0.016 mg/kg and @ 0.025mg/kg intravenously to group II. Blood sampling was done before administration of vincristine sulphate and on every 5thday of administration i.e. on day 0, 5, 12 and 19 in both the groups. Haematological and blood biochemical parameters were evaluated and all the dogs were monitored regularly for adverse effects of the drug throughout the study. There was significant fall in haemoglobin in group II and non significant fall in TLC and rise in total platelets count in both the groups indicating thrombocytosis. In both the groups, there were few adverse clinical signs suggesting of mild gastrotoxicity by the drug. Alterations in blood biochemical parameters like ALT, ALP, GGT and others indicate mild hepatotoxicity.

Key words: Dogs, Gastrotoxicity, Hepatotoxicity, Vincristine sulphate

Vincristine is a plant alkaloid obtained from plant *Vinca rosea*. It is a chemotherapeutic agent widely used to treat various neoplastic disorders, such as lymphomas, leukemias and sarcomas in dogs and cats (Dobson *et al.*, 2008). It has a wider application in veterinary medicine in combined chemotherapy with other anti-cancerous drugs. The main mechanisms of vinca alkaloid cytotoxicity is due to their interactions with tubulin and disruption of microtubule function, particularly of microtubules comprising the mitotic spindle apparatus, directly causing metaphase arrest (Himes, 1991). In an ideal situation, a chemotherapy drug would kill cancer cells in an animal's body without harming normal healthy cells but this does not happen. One of the primary goals of cancer treatment in veterinary patients is to preserve quality of life. Every effort is made to minimize adverse effects of chemotherapy, but it is not possible to eliminate them completely. No work has been done on this aspect so, the study was conducted to know the effects of vincristine sulphate on various haematological and blood biochemical parameters.

MATERIALS AND METHODS

The present study was conducted on 10 clinically healthy adult mongrel dogs weighing 10-20 kg irrespective of age and sex which were randomly divided into two groups comprising of five animals in each group. Group 1dogs (n=5) were given vincristine sulphate at the dose rate of 0.016 mg/kg and Group 2 dogs (n=5) at the dose rate of 0.025 mg/kg, intravenously once a week for three weeks. Blood sampling was done before administration of vincristine sulphate and on every 5th day of drug administration i.e., on days 0, 5, 12 and 19.

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Clinical observations: For the entire period of the study, all the dogs were monitored regularly for various clinical observations like restlessness, lethargy, loose stool, urinary incontinence, forgetfulness, lameness, shivering /shaking, vomiting and diarrhoea.

Blood samples were collected in EDTA vials for haematology and in 3.8% sodium fluoride vials for glucose estimation. Vials without any anticoagulant were used 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 3000 rpm 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 analyzer (Agappe Diagnostics Ltd., India) with ready to use kits from Transasia Ltd. (Transasia Bio Medicals Ltd., India).

To evaluate the effect of vincristine sulphate on various systems, following parameters were estimated at various intervals as mentioned above. The haematological parameters included 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), and serum biochemical parameters included glucose, triglycerides, total cholesterol, lactate dehydrogenase (LDH), alanine

aminotransferase (ALT), 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. The study was conducted after the approval of Institutional Animal Ethical Committee of the university.

RESULTS AND DISCUSSION

In both the groups, none of the dogs exhibited any adverse clinical signs after administration of vincristine sulphate except one dog suffered anorexia and lethargy for one day at second dose of drug administration (Table1).

Table 1
Various clinical signs observed during entire period of study

Clinical Observations	Total number of dogs affected					
	After Ist dose of drug		After 2nd dose of drug		After 3rd dose of drug	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Restlessness	0	0	0	0	0	0
Lethargy	0	0	1	1	0	0
Loose stool	0	0	0	0	0	0
Urinary incontinence	0	0	0	0	0	0
Forgetfulness	0	0	0	0	0	0
Lameness	0	0	0	0	0	0
Shivering /Shaking	0	0	0	0	0	0
Vomiting	0	0	0	0	0	0
Diarrhoea	0	0	0	0	0	0
Appetite loss	0	0	1	1	0	0

The nausea following chemotherapy is hypothesized to be produced through activation of the chemoreceptor trigger zone (CTZ) around the 4th ventricle (Holland *et al.*, 1977). Amber *et al.* (1990) reported similar clinical observations i.e. transient anorexia and no other toxicity in dogs receiving chemotherapy with vincristine sulphate (0.5 mg/M^2 BSA) weekly) against canine transmissible venereal tumor.

No significant changes were observed in any of the haematological parameters in group I animals, except a significant decline in MCH values on days 5 and 12 post-therapy as compared to day 0. There was a significant decline in Hb and MCH values in group II on day 19 post-therapy as compared to day 0. In both the groups, TLC and TEC decreased and total platelet levels increased non-significantly. A non-significant increase in MCV on days 12 and 19 post-therapy as compared to day 5 and non-significant decline in MCHC was there on day 12 as compared to day 0 in both the groups (Table 2 & 3). The decreasing pattern of haemoglobin and TLC may be consequential to bone marrow suppressive effect of cytotoxic drugs affecting erythropoiesis and myeloid cell line (Morse and Stohlman, 1996; Sandhu and Ramphal, 2006). Marks (20l6) reported that macrocytosis (increase in MCV) correlates with the regenerative anaemia. Most regenerative anaemias have an increased MCV and a MCHC. Thrombocytosis following administration of vinca alkaloids has been reported repeatedly in dogs (Park *et al.*, 2015). Several hypotheses have been suggested for this rise. The most plausible one could be that vincristine accelerates megakaryocytic breakdown and stimulates

Table 2
Effect of vincristine sulphate on haematological parameters at group I dogs (Mean ±S.E., n=5)

Parameters (Units)	Before drug admn. (Day 0)	At 5th day of 1st dose (Day 5)	At 5th day of 2nd dose (Day 12)	At 5th day of 3rd dose (Day 19)
Haemoglobin (g/dl)	12.24^{a} ± 0.34	11.74^{a}±0.50	11.58^{a}±0.21	11.36^{a}±0.25
Packed cell volume (%)	38.42^{a}±0.71	37.68^{a}±1.07	38.34^{a}±0.53	36.80^{a}±0.94
TEC (x106/mm3)	6.04^{a}±0.37	6.96^{a}±0.40	6.21^{a}±0.19	6.05^{a}±0.32
TLC (x103/mm3)	12.79^{a}±1.44	12.27^{a}±1.81	11.66^{a}±1.31	10.29^{a}±1.11
MCV (fl)	60.40^{a}±2.95	56.55^{a}±4.24	61.80^{a}±2.50	59.94^{a}±2.50
MCH (pg)	19.2^{b}±0.88	17.63^{ab}±1.42	18.69^{a}±0.90	18.55^{ab}±0.11
MCHC (g/dL)	31.84^{a}±0.38	31.11^{a}±0.51	30.22^{a}±0.68	30.88^{a}±0.25
Total platelets count (x103/mm3)	406.40^{a}±52.07	406.40^{a}±95.51	423.00^{a}±75.13	467.60^{a}±79.99
Neutrophils (%)	66.60^{a}±1.69	65.20^{a}±3.50	64.80^{a}±1.16	64.80^{a}±1.77
Eosinophils (%)	3.00^{a}±0.89	4.00^{a}±1.05	4.20^{a}±0.58	4.80^{a}±0.97
Basophils (%)	1.00^{a}±0.55	1.60^{a}±0.68	0.80^{a}±0.37	1.20^{a}±0.58
Lymphocytes (%)	26.20^{a}±2.85	25.40^{a}±1.28	26.60^{a}±0.51	24.60^{a}±1.21
Monocytes (%)	3.40^{a}±1.12	3.80^{a}±1.16	3.60^{a}±0.68	4.60^{a}±1.03

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

Table 3
Effect of vincristine sulphate on blood biochemical parameters group II dogs (Mean±S.E., n=5)

Parameters (Units)	Before drug admn. (Day 0)	At 5th day of 1st dose (Day 5)	At 5th day of 2nd dose (Day 12)	At 5th day of 3rd dose (Day 19)
Haemoglobin (g/dL)	13.32^{a}±0.18	12.70^{b}±0.15	11.92^{a}±0.24	11.44^{a}±0.29
Packed cell volume (%)	38.24^{a}±0.53	36.80^{a}±0.93	37.22^{a}±0.61	36.48^{a}±1.01
TEC (x106/mm3)	6.41^{a}±0.28	6.77^{a}±0.38	6.24^{a}±0.25	6.19^{a}±0.35
MCV (fl)	59.56^{a}±1.67	56.63^{a}±3.404	60.15^{a}±1.93	60.88^{a}±3.17
MCH (pg)	20.74^{b}±0.52	19.00^{ab}±1.16	19.27^{ab}±0.68	19.22^{a}±1.47
MCHC (g/dL)	34.84^{a}±0.38	33.59^{a}±0.15	32.03^{a}±0.44	31.46^{a}±1.27
TLC (x103/mm3)	11.47^{a}±0.82	10.11^{a}±0.43	9.64^{a}±1.04	9.07^{a}±0.52
Total platelets count(x103/mm3)	364.00^{a}±24.7	425.60^{a}±55.73	505.00^{a}±84.34	571.20^{a}±55.49
Neutrophils (%)	64.60^{a}±1.83	61.00^{a}±2.86	59.80^{a}±0.58	61.00^{a}±1.22
Eosinophils (%)	4.40^{a}±0.93	5.40^{a}±0.51	6.00^{a}±0.31	5.80^{a}±0.58
Basophils (%)	1.20^{a}±0.49	1.60^{a}±0.24	2.00^{a}±0.31	1.60^{a}±0.24
Lymphocytes (%)	25.00^{a}±2.30	25.60^{a}±2.11	26.60^{a}±0.98	25.80^{a}±2.26
Monocytes (%)	4.80^{a}±0.58	6.40^{a}±0.60	5.60^{a}±0.51	5.80^{a}±0.97

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

thrombopoiesis (Ahn *et al.*, 1978).

Mealy (2008) reported that at standard dosages (0.5–0.7 mg/m^2) vincristine sulphate is not usually myelosuppressive in dogs. Yadav (2014) and Rocha *et al.* (2016) reported that no significant leucopenia or change in RBC levels were seen in dog treated with vincristine sulphate against CTVT, suggesting that vincristine sulphate has low toxicity on these cells. Rocha *et al.* (2016) reported that no significant leucopenia or change in RBC levels were seen in dog treated with vincristine sulphate against CTVT, suggesting that vincristine sulphate has low toxicity on these cells.

With respect to the serum biochemical parameters, in both the groups, there was increase in levels of glucose on day 5 post-therapy as compared to day 12 in both the groups which may be due to increase in cortisol level in the blood. Cortisol counters insulin by encouraging higher blood sugar and stimulating gluconeogenesis (Toshihiko *et al.*, 1996). There was a significant increase in ALT, ALP, LDH and CK levels. A non significant increase in GGT levels was there in group I, but in group II, this increase was a significant one. In both the groups, significant rise in ALP was seen but in group I, at 3rd dose of drug administration ALP level declined to that of day 0.

The initial rise and later on decrease might be because of the reason that after acute severe hepatic necrosis, ALP activity increases 2-5 folds in dogs and cats, stabilizes and then gradually declines over 2-3 weeks (Kahn and Line, 2010). A non significant increase in GGT was noticed with each consecutive administration of drug that is a more specific marker of liver damage in dogs than ALP. This simultaneous rise in ALT, ALP and GGT suggests cytotoxic effects of chemotherapy on liver (Camacho and Laus, 1989). In both the groups, a rise in the level of LDH was recorded from day 0 to day 19 post-therapy. LDH activities are high in various tissues of body. Therefore, measurements of LDH are not organ specific (Velberg, 2008). There are reports of necrotizing myopathy caused by vincristine sulphate in humans (Quintrec and Quintrec 1991) and this could be a reason of increase of CK values on day 19 post-therapyduring the study (Table 4 and 5).

An undulating pattern was seen with values of direct bilirubin in group I. However, in group II, a non significant but continuous rise was seen in values of direct bilirubin. The pattern of bilirubin could be because of hepatic and biliary excretion of vincristine in normal dogs (Maddison *et al.*, 2008). In group I, a continuous non significant decline in A:G ratio was there, while in group II, this decline was only present on days 5 and 12 post-therapy. This decline in A:G ratio was suggestive of acute liver injury (Benjamin, 1979). In both the groups, there was a non significant rise in creatinine, BUN and urea levels. These changes could be ascribed to transient renal dysfunction after chemotherapy (Eleanor and David, 1982). There was a significant increase in potassium at day 12 in group 2 as compared to day 0 and this could be due to cytotoxicity caused by drug (Gadmade, 2006). Other parameters did not vary significantly throughout the experiment (Table 4 & 5). On the basis of clinical observation, haematological and blood biochemical study, vincristine sulpahte seems to be mild gastrotoxic and mild hepatotoxic in dogs.

Table 4
Effect of vincristine sulphate on blood biochemical parameters group I dogs (Mean±S.E. , n=5)

Parameters (Units)	Before drug admn. (Day 0)	At 5th day of 1st dose (Day 5)	At 5th day of 2nd dose (Day 12)	At 5th day of 3rd dose (Day 19)
Glucose (mg/dL)	112.75^{a}±4.44	149.88^{b}±5.61	108.37^{a}±14.90	85.12^{a}±11.87
Triglycerides (mg/dL)	24.76^{a}±2.92	25.55^{a}±2.57	23.71^{a}±1.36	22.05^{a}±1.65
Total cholesterol(mg/dL)	156.28^{a}±12.21	163.45^{a}±15.78	170.02^{a}±13.22	151.59^{a}±5.82
LDH (IU/L)	110.69^{a}±13.39	118.58^{a}±11.83	131.27^{a}±14.27	189.74^{b}±26.46
ALT/SGPT (IU/L)	28.52^{a}±1.90	44.29^{b}±3.86	46.45^{b}±3.09	48.10^{b}±8.85
ALP (IU/L)	33.45^{a}±1.80	38.81^{ab}±0.50	44.26^{b}±3.47	33.45^{ab}±2.13
GGT (IU/L)	3.80^{a}±0.69	4.37^{a}±0.71	5.53^{a}±0.84	5.73^{a}±0.60
Creatine kinase (IU/L)	72.92^{a}±6.25	105.79^{ab}±12.55	112.90^{b}±11.56	195.10^{c}±8.54
Direct bilirubin (mg/dL)	0.20^{a}±0.10	0.25^{a}±0.04	0.09^{a}±0.24	0.40^{a}±0.16
Total protein (g/dL)	5.42^{a}±0.01	5.38^{a}±0.20	5.56^{a}±0.25	5.60^{a}±0.35
Albumin (g/dL)	2.85^{a}±0.10	2.34^{a}±0.30	2.47^{a}±0.12	2.61^{a}±0.36
Globulin (g/dL)	2.57^{a}±0.10	3.04^{a}±0.43	3.08^{a}±0.24	2.98^{a}±0.30
A:G ratio	1.19^{a}±0.04	0.88^{a}±0.20	0.82^{a}±0.10	0.92^{a}±0.15
BUN(mg/dL)	10.51^{a}±1.03	10.19^{a}±0.93	10.60^{a}±0.68	12.35^{a}±1.92
Urea (mg/dL)	22.49^{a}±2.20	21.81^{a}±2.00	22.69^{a}±1.46	26.43^{a}±4.10
Creatinine (mg/dL)	1.17^{a}±0.52	1.31^{a}±0.94	1.32^{a}±0.67	1.32^{a}±0.51
Sodium (mmol/L)	141.44^{a}±0.34	144.28^{a}±2.83	140.82^{a}±0.89	142.72^{a}±2.71
Potassium (mmol/L)	4.33^{a}±0.23	4.18^{a}±0.27	4.43^{a}±0.52	4.29^{a}±0.33
Chloride (mmol/L)	116.96^{a}±1.68	117.64^{a}±3.24	122.42^{a}±2.65	118.32^{a}±2.27
Calcium (mmol/L)	2.83^{a}±0.10	2.75^{a}±0.14	3.04^{a}±0.22	3.16^{a}±0.09
Cortisol (µg/ dL)	1.21^{a}±0.06	1.45^{a}±0.20	1.27^{a}±0.08	1.38^{a}±0.09

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

Table 5
Effect of vincristine sulphate on blood biochemical parameters group II dogs (Mean ±S.E., n = 5)

Parameters (Units)	Before drug admn. (Day 0)	At 1st dose of drug (Day 5)	At 2nd dose of drug (Day 12)	At 3rd dose of drug (Day 19)
Glucose (mg/dL)	116.87^{a}±7.46	167.16^{b}±6.49	105.62^{a}±14.33	108.81^{a}±16.82
Triglycerides (mg/dL)	24.00^{a}±2.85	20.97^{a}±1.98	22.43^{a}±2.21	23.59^{a}±2.63
Total cholesterol(mg/dL)	153.01^{a}±11.11	163.83^{a}±10.71	156.12^{a}±12.64	148.74^{a}±7.10
LDH (IU/L)	118.95^{a}±6.45	125.77^{a}±16.99	143.12^{a}±13.17	185.88^{b}±13.96
ALT (IU/L)	22.10^{a}±2.22	38.95^{b}±1.64	45.73^{b}±4.08	57.93^{c}±4.46
ALP (IU/L)	33.11^{a}±1.25	46.67^{b}±3.47	49.50^{b}±2.30	60.17^{c}±4.87
GGT (IU/L)	3.73^{a}±0.55	5.44^{a}±0.54	7.97^{b}±0.88	8.23^{b}±1.10
Creatine kinase (IU/L)	74.79^{a}±5.43	88.92^{a}±6.74	128.4^{b}±15.74	150.50^{b}±18.55
Direct bilirubin (mg/dL)	0.09^{a}±0.03	0.12^{a}±0.02	0.21^{a}±0.14	0.25^{a}±0.16
Total protein (g/dL)	5.68^{a}±0.23	5.28^{a}±0.46	5.36^{a}±0.50	5.64^{a}±0.47
Albumin (g/dL)	2.84^{a}±0.11	2.43^{a}±0.17	2.42^{a}±0.26	2.91^{a}±0.21
Globulin (g/dL)	2.84^{a}±0.12	2.86^{a}±0.32	2.94^{a}±0.26	2.73^{a}±0.27
A:G ratio	0.100^{bc}±1.00	0.88^{ab}±0.67	0.82^{a}±0.58	1.08^{c}±0.38
BUN (mg/dL)	11.60^{a}±2.17	11.80^{a}±1.16	12.80^{a}±1.19	11.61^{a}±0.80
Creatinine (mg/dL)	1.30^{a}±0.51	1.85^{a}±0.29	1.69^{a}±0.21	1.50^{a}±0.16
Urea (mg/dL)	24.84^{a}±4.64	25.25^{a}±2.48	27.40^{a}±2.55	24.84^{a}±1.71
Sodium (mmol/L)	141.62^{a}±0.45	141.60^{a}±1.04	142.02^{a}±0.51	143.93^{a}±3.00
Potassium (mmol/L)	4.43^{ab}±0.11	4.21^{a}±0.28	5.07^{b}±0.25	4.96^{ab}±0.34
Chloride (mmol/L)	117.42^{a}±1.69	112.04^{a}±2.44	133.36^{a}±1.48	118.86^{a}±3.02
Calcium (mmol/L)	3.07^{a}±0.32	2.57^{a}±0.14	2.81^{a}±0.27	2.95^{a}±0.24
Cortisol (µg/ dL)	1.33^{a}±0.09	1.42^{a}±0.11	1.35^{a}±0.08	1.24^{a}±0.08

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

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