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EFFECTS OF DIFFERENT DOSES OF MEDETOMIDINE ON CLINICAL AND HEMATOLOGICAL PARAMETERS IN DOGS

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ABSTRACT

Medetomidine HCl was clinically evaluated as anesthetic at various doses on the basis of sedative, analgesic and hematologic effects in mongrel dogs under experimental conditions. Clinically healthy dogs (n=50) divided randomly in groups A, B, C, D and E (n=10, each) were injected with normal saline and 15, 30, 45 and 60 µgm/Kg body weight medetmidine HCl, respectively. It was noticed that body temperature, pulse and respiratory rates tends to decrease overall at various doses in treated dogs compared to control. Blood pressure of the dogs in experimental groups showed slight decline in values than control. Extent of sedation and analgesia was more prominent at higher doses. Maximum decrease of Serum alkaline phosphatase (SAP) concentration was observed in group B (131.4±10.2; 133.2±22.5) at 20 and 40 minutes post drug administration and at 60 minutes (125.4±10.0) in group E. The highest fall in Aspartate transaminase (AST) values was seen in group E (31.6±2.4, 34.2±2.8 and 35.9±2.0) at 20, 40 and 60 minutes. Alanine transaminase (ALT) values significantly declined in dogs of group B (42.5±9.1, 34.7±6.5 and 35.9±8.0) in relation to selected timings. Urea levels differed non-significantly with control and decrease in creatinine level was significant in groups E (0.67±7.8). D (0.85±.29) and B (0.97±.22) compared to control. At 20, 40 and 60 minutes post drug administration value of uric acid increased significantly in group D (0.74±0.11), B (0.67±17) and C (0.73±.11) than control. At different time intervals post anesthetic administration hemoglobin levels in group D was 11.95±1.47, 12.08±1.12 and 12.9±2.47 which showed significant difference with control (14.01±1.37). Non-significant differences were observed in values of total leucocytes count (TLC), differential leucocytes count (DLC) and erythrocyte sedimentation rate (ESR) in dogs of treated and control groups with different doses in relation to time. Results depicted that in group B (15µgm/Kg body weight) parameters recorded were efficient to declare the dose of drug safe for maintenance of anesthesia with no side effects.

Key words: Anesthesia, Sedation, Analgesia, Recovery, Hematology and Medetomidine HCl

INTRODUCTION

A surgical manipulation requires extensive effort to prevent or eliminate pain in both human and animal patients. An ideal surgical anesthesia is a state of central nervous system depression, characterized by the loss of all sensations and consciousness. It is required for humane surgical procedures and efficacy of surgery (De Moor, 2010)**.**

Medetomidine HCl, an alpha-2 adrenoceptor agonist is a potent sedative-analgesic (Savola *et al.,* 1986). The alpha-2 adrenoreceptors inhibit release of nor-adrenaline, acetyl choline, serotonin, dopamine, substance P and other neurotransmitters suppress neuronal excitability, cause sedation, anti-nociception, hypotension and bradycardia (Aantaa *et al*., 1995). Medetomidine HCl produces reliable degree of sedation, muscle relaxation and analgesia in different animal species (Weinbroum and Abraham, 2001; Ripamonti *et al.,* 2001). Barbiturates (Robinson *et al*., 1986), Ketamine HCl (Verstegen *et al*., 1995) and Chloral hydrate (De Moor, 2010) are other anesthetics used in dogs, cats and large animals, respectively. Major side effects include muscle turgidity, fluctuation in heart's functionality and very narrow safety margin (Hellebrekers *et al.,* 1998). Decrease in body temperatures is a salient feature of medetomidine (Pypendop and Vertegen, 1994). The decrease in body temperatures can be due to direct effect on noradrenergic hypothalamus involved in thermoregulation (Virtanen, 1989). It has been estimated that each year over 7 million veterinary patients use α-2 adrenoreceptor agonist as part of their anesthetic protocol (Maze and Trangilli 1991). The α-2 adrenoreceptor agonist potentiate anesthesia to produce reliable sedation and analgesia (Vainio, 1989). Schmeling (1991) and Salmenpera (1994) reported hemodynamic effects of parentally administered medetomidine in dogs and explained dose response relationship.

Medetomidine administered parenterally results in a dose dependent response on hemodynamic parameters (Schmeling *et al*., 1991; Salmenpera *et al*., 1994). Drug is frequently used in dogs/cats (Golden *et al.,* 1998; Lamont *et al.,* 2001) and at limited level in sheep (Celly *et al*., 1999), cattle (Bryant *et al.,* 1998), buffalo (Kalhoro *et al*., 2000) and goats (Kinjavdekar *et al.,* 2007). Present

experiment was designed to evaluate the sedative and analgesic effects of medetomidine at different dose rates in dogs. Anesthetic effects on respiration, blood pressure, temperature and hematological parameters of dogs were evaluated.

MATERIALS AND METHODS

Efficacy and suitability of medetomidine HCl anesthetic was evaluated in mongrel dogs under experimental conditions including sedation, analgesia and hematological indices in relation to time. Clinically healthy mongral dogs (n=50) of either sex, age (1 to 4 years) and weight (20 to 30 kg) were randomly divided in five groups (n=10 each). The dogs were procured from local areas in and around Lahore city and housed in kennels at the Surgery Section, Department of Clinical Medicine and Surgery, UVAS, Lahore. Medetomidine HCl having concentration 10 mg/ml (Domitor; Orion Corp. Orion Pharm. Dept; Finland) available as colorless, clear and aqueous solution (10 ml) was procured from market.

Experimental plan: Medetomidine HCl was administered to dogs of groups B, C, D and E at dose rate of 15, 30, 45 and 60µg/Kg body weights intravenously. Group A, (control) was injected with normal saline 0.9%. Temperature, pulse, respiration, blood pressure, liver enzymes, urea level, creatinine/uric acid concentrations and hematological indices were recorded at 20, 40 and 60 minutes including all dogs of different groups. Sedation and analgesia was evaluated on the basis of presence/absence of body reflexes. Head down, saliva drooling, jaw tone, palpebral blinking and coordination reflexes were included for assessment of sedation level. The reflexes for analgesia evaluation were ear twitch, toe pinch, tail pinch, anal and patellar. The scoring system for degree of sedation/analgesia was chalked out as described by Pettifer and Dyson (1993).

Biological observations: Physiological parameters including temperature, pulse, respiration and blood pressure were recorded manually for each of the dogs at 20, 40 and 60 minutes following the scheme described by Venugopalan (1998). Scoring system was adopted with certain modifications to analyze the extent of sedation and analgesia (Abd-Almaseeh, 2008; Keniya, 2011). Experimental dogs without loss of any of the included reflexes were scored zero. Dogs showing loss of 1-2 reflexes with mild sedation and analgesia were scored 1-2. While animals with loss of 3-4 reflexes of sedation or analgesia were scored 3-4 and loss of 5-6 reflexes were scored 5-6. Nature of induction was recorded as either smooth/effortless or struggling. Onset, duration of recumbency and nature of recovery were recorded. Liver function was evaluated by measuring enzymes in sera of experimental animals at different dose levels in relation to time. The SAP, AST and ALT were measured using commercially available kits (Crescent Diagnostics, Saudi Arabia) having Cat # CZ901U, CZ904L and CZ902L, respectively. Urea, creatinine and uric acid levels were monitored to evaluate the effect of drug on kidney function. Level of urea was measured by Urease-GLDH enzymatic UV test using a commercially available kit "Urea UV" (Merck Pvt. Limited, France, Ref. # 5.17610.0001). Serum creatinine concentration was determined by Kinetic method without de-proteinization–Jaffe reaction using "Creatinine Test Kit" (Crescent Diagnostics, Saudi Arabia; Cat. # CS604-8). Uric acid was measured by Uricase/PAP method using "Globals's Uric Acid Kit" (Global Invitro LLP, London, UK. Ref. # UAC62150). Hemoglobin concentration, total leukocyte count, differential leukocyte count and erythrocyte sedimentation rate were determined using automated hematology analyzer (Abacus Junior Vet Serial No 130076 Austria) at University Diagnostic Laboratory.

Statistical Analysis: Data on selected parameters for both control and treated groups were recorded and analyzed using one way ANOVA by statistical software package (SPSS) version 13.00. Different group means were compared by Duncan's Multiple Range (MDR) post hoc test at a probability (P) level ≤0.5.

RESULTS

Efficacy of medetomidine HCl anesthetic was assessed under experimental conditions in dogs on the basis of physiological and hematological parameters.

Effects on physiology: Body temperature decreased in all groups after administration of medetomidine HCl. Hypothermia in group B (15 µgm/kg BW) was significant than control (A) at 20, 40 and 60 minutes, respectively. There was non-significant difference regarding body temperature between other treatment groups with respect to time intervals. Pulse rate decreased significantly below baseline values ($P<0.05$) in all groups except control. During anesthesia at 20 minutes interval there was no difference amongst five treatment groups regarding respiratory rate values. At 40 and 60 minutes post drug administration, there was significant ($P<0.05$) fall in respiratory rate among all treated groups compared to normal. Treatment group C differed significantly with other treatment and control groups in respiratory rate. Significant fall in diastolic blood pressure values at 20, 40 and 60 minutes intervals during anesthesia was observed in treatment groups B and C. The value of systolic blood pressure decreased significantly at 20 minutes post drug administration in groups B and C compared to A (Table 1). At 60 minutes interval, systolic blood pressure in dogs of group B differed significantly ($P<0.05$) with those of groups A and E. Dogs of group C and D differed non-significantly with control (Table 01).

Sedation and analgesia: Smooth pattern of induction was observed in all of the treated groups. None of the animals showed struggling and shivering during induction. The dogs lowered their heads, bent knees and gently lay down on ground. No sign of staggering gait, discomfort and distress during induction was present. Overall the induction of anesthesia was effortless without any sign of discomfort/excitement but time for achieving sedation and analgesia differed significantly among all treatment groups. The shortest induction time was observed in dogs of group E (60µgm/kg) followed by groups D, C and B, respectively. Maximum length of recumbency period was noticed in dogs of group E followed by D, C and B, respectively. Longest recovery time was noted in dogs of group E followed by groups D, C and B, respectively. The degree of sedation was higher at higher doses of medetomidine HCl. In group B (15µgm/kg BW), there was mild sedation and moderate in C. The dogs of group D showed moderate sedation in 4 and deep sedation in 6 dogs. Treatment group E (60µgm/kg BW) produced deep sedation in all the animals (Table 3). The dose rate of 15µg/kg BW produced mild skin analgesia as only 1-2 reflexes disappeared. The dogs of group C exhibited moderate analgesia (Table 2). The dogs of group D and E administered with medetomidine HCl exhibited moderate to deep analgesia. In group A (control), all reflexes were present and no analgesia was seen.

Liver and kidney functions: The SAP values in dogs all treated groups at 20, 40 and 60 minutes during anesthesia showed significant difference ($P<0.05$) compared to control. However, the difference amongst the treated groups was non-significant suggesting that the SAP values were not affected by increase in the dose of the anesthetic agent. The value of AST was found to be dependent on the dose of anesthetic used. At 20 minutes post drug administration maximum decrease in enzyme concentration was observed in group E and it differed significantly ($P<0.05$) with control and other treated groups. At 40 minutes, the highest fall in AST values was seen in group E and it showed significant difference with control group A. At 60 minutes post anesthetic drug administration group C, D and E showed significant difference ($P<0.05$) in AST values with groups A and B (Table 4). The concentration of ALT was dependent on the dose of anesthetic used. At 20, 40 and 60 minutes post drug administration highest decline in ALT was seen in dogs of group B and it showed significant difference with rest of the groups.

At 20 minutes major decline in urea levels was assessed in group D dogs, followed by C, B and E, respectively (Table 4). At 40 minutes highest drop in urea levels was detected in dogs of group C which differed significantly with A, B, D and E. At 20 minutes post drug administration, the change in creatinine enzyme was only significant in group E compared with control while non-significant with rest of the groups. At 40 minutes and 60 minutes differences in the creatinine values amongst the control and treatment groups were non-significant ($P>0.05$). At 20 minutes post drug administration value of uric acid increased significantly in group D than normal and rest of the treated groups. At 40 and 60 minutes increase in blood uric acid values was non-significant amongst all groups compared with control (Table 2).

Hematology: A very slight decline in hemoglobin concentration of blood was noticed in dogs after injection of medetomidine HCl at various doses. At 20 minutes post anesthetic administration hemoglobin level was decreased significantly in group D ($p<0.05$) compared with control and group B. At 40 and 60 minutes post administration of anesthetic drugs the dogs showed non-significant change in hemoglobin levels. Mostly non-significant variation of TLC was observed in dogs of treated and control groups with different doses in relation to time. At 40 minutes the value of TLC increased significantly in dogs of group E but not in group B. At 60 minutes, all the treated groups differed significantly with control group A. The DLC level of dogs monitored at 20, 40 and 60 minutes post administration of medetomidine HCl at variable doses showed a non-significant change ($P>0.05$) in control and treated dogs. The values of ESR at 40 minutes post administration of anesthetic drug showed a significant decline compared with dogs of group E and B but non-significant ($P>0.05$) when compared with control. At 60 minutes the dogs of all groups showed significantly different levels of ESR compared to dogs of control group.

Table 01. Effect of medetomidine HCl anesthetic on temperature, pulse, respiration, diastolic and systolic blood pressures of experimental dogs in relation to time.

Groups	Treatments	Temperature degree farenheit			pulse per minute			Respiration per minute			Systolic blood pressure, beats per minute			Diastolic blood pressure, beats per minute		
		20 mins	40 mins	60 mins	20 mins	40 mins	60 mins	20 mins	40 mins	60 mins	20 mins	40 mins	60 mins	20 mins	40 mins	60 mins
A	Control	101.5±.22b^{c}	101.9±.37^{c}	101.7±.22^{c}	75.1±3.6$_{bc}$	74.8±3.4^{bc}	77.9±3.54^{c}	18.5±1.4^{a}	19.0±1.1^{b}	17.9±2.2^{b}	102.0±7.5^{b}	117.0±6.3^{b}	113.5±7.8^{b}	74.0±6.6^{c}	75.5±6.85^{a}	70.5±8.3^{b}
B	15µg/kg	100.7±.41^{a}	100.4±.62^{a}	100.3±.52^{a}	72.8±3.8^{b}	72.1±2.76^{ab}	72.4±8.6^{ab}	17.0±1.8^{a}	16.4±1.6^{a}	16.1±2.1^{ab}	102.5±7.9$_{a}$	110.5±6.8^{a}	105.0±8.2^{a}	52.5±7.9^{a}	71.0±9.9^{a}	56.0±9.4^{a}
C	30 µg/kg	101.7±.13^{c}	101.3±.26^{b}	101.2±.20^{b}	67.5±1.9^{a}	69.9±1.7^{a}	68.9±2.0^{a}	17.0±1.8^{a}	16.9±1.7^{a}	15.5±1.9^{a}	100.0±9.4^{a}	110.5±6.4^{a}	103.0±7.9^{a}	63.0±11.6^{b}	73.0±6.7^{a}	59.5±20.1^{ab}
D	45 µg/kg	101.6±.19b^{c}	101.5±.32^{b}	101.5±.36b^{c}	73.5±3.4^{bc}	73.1±3.17^{b}	72.8±4.5^{ab}	18.5±1.3^{a}	17.1±1.8^{a}	16.7±2.1^{ab}	110.0±9.1^{b}	112.0±5.9a^{b}	106.5±8.2a^{b}	67.5±12.7^{bc}	72.0±12.3^{a}	67.0±9.5^{ab}
E	60 µg/kg	101.4±.26^{b}	101.4±.22^{b}	101.4±.22b^{c}	76.2±3.1^{c}	76.0±3.4^{c}	76.5±2.8^{bc}	17.5±2.0^{a}	16.9±2.6^{a}	16.00±1.0^{ab}	110.5±6.8^{b}	110.0±0.0^{a}	109.0±5.8^{ab}	70.0±6.6^{bc}	69.0±7.4^{a}	68.0±7.9^{b}

Means carrying same superscripts differed non-significantly (p>o.o5), and having different superscripts differed significantly (p<0.05).

Table 02. Effect of medetomidine HCl as anesthetic on liver and kidney functions in relation to time.

Groups	Treatments	SAP IU/L			AST IU/L			ALT IU/L			UREA(mg/dl)			CREATININE(mg/dl)			URIC ACID(mg/dl)		
		20 mins	40 mins	60 mins	20 mins	40 mins	60 mins	20 mins	40 mins	60 mins	20 mins	40 mins	60 mins	20 mins	40 mins	60 mins	20 mins	40 mins	60 mins
A	Control	207.7±4.5^{c}	220.8±17.9^{b}	220.8±17.9^{c}	73.6±12.4^{c}	70.6±9.3^{b}	70.6±9.3^{c}	66.2±2.8^{c}	64.7±7.2^{d}	56.1±5.15^{c}	16.1±2.3^{c}	19.9±4.4^{ab}	16.2±2.1^{a}	0.81±0.33^{a}	0.93±0.37^{a}	0.98±0.30^{a}	0.50±0.26^{a}	0.54±0.17^{a}	0.63±0.25^{a}
B	15µg/kg	131.4±10.2^{a}	133.2±22.5^{a}	166.7±27.8^{b}	40.9±3.3^{b}	39.2±4.5^{a}	42.5±4.3^{b}	42.5±9.1^{a}	34.7±6.5^{a}	35.9±8.0^{a}	14.5±1.6^{abc}	19.0±5.5^{ab}	15.9±3.5^{a}	0.70±0.15^{a}	0.94±0.24^{a}	0.97±0.22^{a}	0.54±0.16^{a}	0.67±0.17^{a}	0.72±0.09^{a}
C	30 µg/kg	132.1±10.5^{a}	134.5±16.5^{a}	133.5±15.2^{a}	37.9±2.8^{b}	35.3±3.1^{a}	36.0±3.3^{a}	49.9±3.5^{b}	49.9±3.5^{c}	45.8±2.3^{b}	13.7±2.0^{ab}	14.4±4.4^{a}	15.3±1.8^{a}	1.06±0.30^{a}	1.02±0.27^{a}	1.00±0.31^{a}	0.57±0.20^{ab}	0.63±0.21^{a}	0.73±0.11^{a}
D	45 µg/kg	135.4±10.5^{a}	147.7±11.8^{a}	132.9±10.4^{a}	35.7±3.7^{ab}	38.9±6.4^{a}	36.2±3.5^{a}	50.2±5.9^{b}	44.1±5.5^{b}	44.7±5.1^{b}	12.8±2.3^{a}	21.9±8.4^{b}	16.3±1.5^{a}	0.90±0.31^{a}	0.85±0.29^{a}	1.29±1.3^{a}	0.74±0.11^{b}	0.62±0.25^{a}	0.56±0.21^{a}
E	60 µg/kg	148.3±8.8^{b}	141.3±10.7^{a}	125.4±10.0^{a}	31.6±2.4^{a}	34.2±2.8^{a}	35.9±2.0^{a}	47.3±4.9^{ab}	44.3±6.3^{b}	45.1±4.5^{b}	15.6±2.3^{bc}	18.4±4.1^{ab}	16.2±2.5^{a}	0.67±7.8^{b}	1.02±0.33^{a}	1.16±0.27^{a}	0.65±0.18^{ab}	0.59±0.17^{a}	0.63±0.15^{a}

Means carrying same superscripts differed non-significantly (p>o.o5), and having different superscripts differed significantly (p<0.05).

Table 03. Effect of medetomidine HCl as anesthetic at different selected doses on hematology of dogs in relation to time.

Groups	Treatments	Hemoglobin (mg/dl)			TLC(10^3/c.mm)			DLC($10_{9/\text{lier}}$)			ESR (mms/hour)		
		20 mins	40 mins	60 mins	20 mins	40 mins	60 mins	20 mins	40 mins	60 mins	20 mins	40 mins	60 mins
A	**Control**	14.01± 1.37^{b}	13.18± 1.93^{ab}	13.44± 1.38^{a}	7.42± 1.0^{a}	7.55± .12^{a}	7.56± .156^{a}	38.09± 17.5^{a}	38.90± 6.80^{a}	36.54± 7.55^{a}	112.63± 4.69^{a}	112.63± 6.10^{ab}	112.81± 5.70^{a}
B	**15µg/kg**	13.9± 1.38^{b}	14.47± 1.55^{b}	14.05± 1.49^{a}	8.10± .50^{a}	8.26± .50^{bc}	8.45± .50^{c}	38.00± 4.5^{a}	43.33± 5.9^{a}	47.11± 5.5^{a}	115.88± 6.29^{a}	120.22± 7.56b	122.88± 5.30^{b}
C	**30 µg/kg**	13.4± 1.65^{ab}	12.96± 1.89^{ab}	13.05± 1.58^{a}	7.83± .50^{a}	7.92± .43^{ab}	8.22± .63^{bc}	40.20± 5.4^{a}	44.10± 6.4^{a}	43.90± 14.2^{a}	106.40± 9.13^{a}	117.30± 7.36^{ab}	121.00± 7.39^{b}
D	**45 µg/kg**	11.95± 1.47^{a}	12.08± 1.12^{a}	12.95± 2.47^{a}	7.74± .22^{a}	7.82± .20^{ab}	7.84± .33^{ab}	37.00± 5.9^{a}	42.90± 8.2^{a}	46.00± 7.7^{a}	108.20± 7.80^{a}	117.70± 6.21^{ab}	122.00± 6.25^{b}
E	**60 µg/kg**	12.7± 1.49^{ab}	12.85± 1.14^{ab}	12.76± 1.08^{a}	7.66± .20^{a}	8.50± .67^{c}	8.59± .70^{c}	41.20± 11.0^{a}	46.90± 10.0^{a}	51.10± 9.5^{a}	109.20± 10.67^{a}	111.00± 6.12^{a}	117.00± 7.74^{ab}

Means carrying same superscripts differed non-significantly (p>o.o5), and having different superscripts differed significantly (p<0.05).

DISCUSSION

Efficacy of medetomidine HCl anesthetic was assessed on the basis of physiological and hematological parameters in dogs under experimental conditions. Slight reduction in rectal temperature of treated dogs was observed with all of the selected doses of medetomidine HCl in present study. In accord lower temperatures were observed in dogs by Virtanen and McDonalds (1985), Kamine *et al*., (2012) using medetomidine HCl. It has been established that Alpha-2 adrenoreceptor inhibitors induce hypothermia and allow better maintenance of body temperature due to peripheral vasoconstriction followed by central redistribution of blood (Pettifer *et al.,* 1993; Vestergen 1993; Pypendop *et al.*. 1998) which is in agreement with findings of present experiment. Following intravenous injection of medetomidine HCl initially there was a fall in pulse rate associated with peripheral vasoconstriction in present study. This vasoconstriction followed by vasodilatation is in line with the pattern augmented by Aghajanain and Rogawski (1983). Medetomidine and other Alpha-2 adrenoceptor agonists induce bradycardia (Vainio *et al.,* 1989; Pypendop *et al.,* 1996). In present experiment, bradycardia was less pronounced in group B, D and E (30, 45 and 60 µgm/kg) than group C (30 µgm/kg) indicating that this effect was not dose dependent. This effect could have been due to the initial combating response of the cardiovascular system of the body. Comparable results have been recorded by Pypendop *et al.* (2000) in dogs regarding the effects of medetomidine on pulse rate. Overall gradual decrease in the respiratory rate was observed in the current study with increasing dose of the drug which may due to decreased oxygen requirement of body owing to fall in muscular activity. Similar findings have been presented previously by Lagerweij *et al.* (1993) and Hammond and England (1994) using medetomidine in dogs and Cullen *et al.* (1993) in cats. Likewise, results of current experiment are strengthened by Vainio *et al.,* (1991) and Hellebrekers *et al.,* (1993).

In present study, systolic blood pressure values decreased appreciably at low doses but at higher doses the effect was minimal which may be due to adaptive cardiac response of the dogs to higher thresh hold of the anesthetic drug. On the contrary a dose dependant effect was recorded for diastolic blood pressure in dogs. In accordance fall in blood pressure by use of α-2 adrenoreceptor was reported by Dyson (1983). Cardiovascular effects had been recorded even at recommended dose (Pypendop *et al*., 1996) which is in agreement with the findings recorded for systolic and diastolic blood pressure compared with control group animals in the current study. Alpha-2 adrenoreceptor agonists induce hypotension and vasoconstriction (Maze and Tranquilli, 1991).

There was significant difference in onset of sedation among various groups in comparison to control in present study. Dose dependent onset of sedation in goats with medetomidine was observed by Kalhoro *et al.,* (2000). In accord with Bruno *et al.* (1998), deepest sedation was recorded with highest dose. Medetomidine HCl is a reliable potent drug for induction of sedation and analgesia (Kamine *et al*. (2012). In present experiment, an approximate duration of sedation recorded was 48 minutes by intravenous administration of 60µgm/kg. An increase in duration and not depth of sedation with increase in dose of medetomidine and other drugs such as acepromazine (Hall and Clarke, 1991) had been recorded. In the present study, medetomidine HCl produced dose dependant levels of sedation and analgesia in dogs. Moderate to deep sedation was observed with 45 and 60 µg/kg dose of medetomidine comparable with findings of Clark and England (1989). All of the four doses of medetomidine used resulted in recumbency in dogs comparable with observations of Kalhoro *et al.* (2000) in goats and buffalo calves. Vainio *et al.* (1989) reported that sedation occurred within 15 minutes of medetomidine administration in dogs. The sedative and analgesic effects appear shortly and last dose-dependently. Signaling pathways in the canine CNS are affected by medetomidine and other alpha-2 adrenoreceptor inhibitors (Stucke *et al.,* 2005). Similar results were reported by Pagel *et al.,* (1998) and Enouri *et al.,* (2008). A calm and quite environment is necessary to achieve maximal dose effects as with all sedative and analgesics (Kramer *et al.,* 1996). In present experiment, higher doses produced very effective, quicker and longer duration of analgesia in dogs. The duration of analgesia was increased with increasing dose of drug in corroboration to the observations of Shahani (1998) in buffalo calves and other species such as in dogs (Clarke and England, 1989; Vainio *et al.,* 1989; Kalhoro *et al.,* 2000). A similar anesthetic drug tramadol seemed to have an analgesic effect in dogs (Giorgi *et al.,* 2009a).

Functioning of liver was assessed by measuring the concentrations of SAP, AST and ALT. At different dose levels of medetomidine in relation to time non-significant differences among treatment groups were observed in current study. Similar findings were recorded by Khan (2003) with use of medetomidine HCl anesthetic. Non-significant change in concentrations of urea, creatinine and uric acid was recorded both in dogs of control and treated groups in present experiment. Slight increase in serum urea level was in agreement with Innes and Nickerson (1970). Medetomidine HCl has diuretic effect due to activation of renal blood volume pressure control system (Guyton, 1981). This may be due to decrease in anti-diuretic hormone (Short, 1992).

There was decrease in values of hemoglobin and change was not significant. Value of TLC seemed to increase with increased dose levels and statically

difference recorded was non-significant. The decrease in values of DLC was highly significant at different dose levels in relation to time. There was non-significant difference between ESR values at different dose levels and time intervals. The value of ESR increased initially but decreased significantly at highest dose used in current experiment. The same picture about decrease of hemoglobin, packed cell volume and total leukocyte count was augmented by Kinjavadekar (2000). PCV and Hb decrease during the anesthesia period was due to shifting of fluid from extravascular to intravascular compartment to maintain normal cardiac output (Wagner *et al.*, 1991). However in horses, Gasthuys *et al.* (1987) observed an increase in PCV 30 min after administration of drug.

In present study, medetomidine HCl proved to be a safe and reliable anesthesia for dogs with minimal effects on various body systems under experimental conditions. It can safely be used for sedation and analgesia in dogs with dose ranging from 15 to 60µgm/kg body weight without any side effect. It is concluded that medetomidine HCl is a highly potent drug which produces effective sedation at lower doses.

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