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Effect of Tramadol Versus Fentanyl on Some Hematological and Serum Biochemical Parameters in Dogs

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ABSTRACT

The present study was designed to compare between the effect of tramadol Hcl and fentanyl citrate on some hematological and serum biochemical parameters in dogs. For this purpose, ten adult mongrel dogs were randomly allocated into two equal groups: Group ı; dogs received tramadol hydrochloride 2 mg kg^{-1} IV; Group ıı; dogs received fentanyl citrate 5 µg kg^{-1} IV. The measured hematological variables were: red blood cell count, packed cell volume, hemoglobin concentration, total leucocytic count, differential leucocytic counts and platelet count. Serum samples were assessed for concentrations of total protein, albumin, glucose, urea, creatinine and serum enzymatic activities of alanine and aspartate transaminases. All parameters were recorded at baseline, following administration of analgesic agents (0 time) and for 1.5 hour later at 15 minutes interval. Data were analyzed using a paired- samples *t*-test ($p < 0.05$). As a result, tramadol induced a significant ($p < 0.05$) decrease in total leukocytic and neutrophil counts while, a significant ($p < 0.05$) increase in total leucocytic, lymphocyte and neutrophil counts were recorded at some time periods in fentanyl group. Blood platelets significantly increased in both groups. Serum urea levels significantly increased in tramadol group while, in fentanyl group, at some periods it showed a significant ($p < 0.05$) decrease as well as creatinine. Red cell parameters as well as other serum biochemical parameters did not show any significant changes in both group. It was concluded that, Fentanyl might have some virtues on leukogarm and some biochemical parameters in dogs. Subsequently, its use may be advantageous over tramadol for canine patient suffering from leukopenia and renal disorders.

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1. INTRODUCTION

Generally, an important axis for minimizing the potential side effects associated with anesthetic procedure in dogs is the production of balanced anesthesia (Heavner, 1996) which can be achieved by incorporation of different classes of analgesic agents into various anesthetic protocols. The use of these analgesics possess several advantages in terms of reducing the amount of anesthetics required to produce surgical anesthesia, stabilizing anesthetic depth, decreasing overall patient morbidity associated with surgery and anesthesia and contributing to reduction of post -operative pain (Muir, 2002; Lamont, 2008). As one of the important class of analgesics in dogs is opioids, it seems necessary to study in depth the effect of individual types of this analgesic category on some hematological and serum biochemical parameter.

Tramadol is a centrally acting 'atypical' opioid analgesic producing a synergistic analgesic effect provided by a µ-opioid receptor affinity coupled with inhibitions of synaptic reuptake of monoamine neurotransmitters such as 5-hydroxytryptamine (5-HT) and norepinephrine (Hennies et al., 1988; Raffa et al., 1992). A product of tramadol's hepatic metabolism, o-desmethyl tramadol (M1), possesses 200–300 times the affinity for µ receptors than tramadol itself (Grond and Sablotzki, 2004).

For post-operative analgesia, preoperative administration of tramadol 2 mg kg-1 IV was previously assessed by Mastrocinque and Fantoni (2003) and results revealed that, at the studied dose tramadol can be used safely to control early pain

following ovariohysterectomy in dogs. Besides, Tramadol has been reported to be an effective analgesic in chronic pain conditions that have opioid resistance (Raffa, 2001).

Administration of tramadol at a dose of 1, 2, and 4 mg kg^{-1} IV did not induce any significant changes in hematology or blood biochemistry (McMillan et al., 2008). Furthermore, no difference was demonstrated in glucose concentration between tramadol and morphine treated dogs when both analgesics were used preemptively to control early postoperative pain in canine ovariohysterectomy (Mastrocinque and Fantoni, 2003).

Fentanyl is a synthetic μ-opioid agonist (Hellyer et al., 2001), opioids are morphine-like compounds that bind to opioid receptors raising pain threshold or decreasing perception of pain by acting at the receptors in the dorsal horn of the spinal cord and mesolimbic system (Yaksh, 1997; Benson, 2002), binding to these receptors resulting in subsequent reduction in release of transmitter substances, such as substance P, dopamine and nor epinephrine thereby inhibiting synaptic transmission of nociceptive input (Inturrisi, 2002; Benson, 2002). There are at least three different opioid receptors: mu, delta, and kappa (μ, δ, κ), analgesia is thought to involve the activation of μ receptors (largely at supraspinal sites) and κ receptors (mainly in the spinal cord) (Heavner and Cooper, 2008).

In clinical circumstances, Fentanyl is particularly suitable as an intraoperative analgesic because of its short onset and duration (Monk et al., 1988; Mendes and Selmi, 2003). Based on its short duration of action, fentanyl should be administered as a constant-rate infusion or as multiple boluses to provide analgesia either in intraoperative or postoperative periods (Hughes and Nolan, 1999).

Opioids may be administered preoperatively without the risk of renal problems or bleeding disorders associated with the use of nonsteroidal anti-inflammatory drugs (Mathews et al., 1996). Furthermore, μ-Agonists tend to produce oliguria in the clinical setting, and this is in part due to increased antidiuretic hormone release leading to altered renal tubular function (Mercadante and Arcuri, 2004).

Administration of fentanyl at a very large doses or prolonged infusions may cause saturation of inactive tissues, with termination of its clinical effects becoming dependent on hepatic metabolism and renal excretion (Gutstein and Akil, 2001). Moreover, prolonged infusions may be associated with a reduction in hepatic blood flow and hence metabolism (Sano et al., 2006).

The purpose of this study was to compare the effect of tramadol Hcl and that of fentanyl citrate on some hematological and serum biochemical parameters in dogs.

2. MATERIALS AND METHODS

Approval to perform the study was obtained from the Ethics Committee of the Faculty of Veterinary Medicine, University of Sadat City.

2.1 Animals

Ten adult mongrel dogs (five males and five females), aged 1.92±0.45 years and weighing 18.24±1.4 kg were selected for this study, dogs were considered to be healthy on the basis of physical examination, complete blood count and blood chemistry profile.

2.2 Experimental design

Animals were randomly allocated into two equal groups (each group included three males and two females): Group ı; dogs were assigned to receive tramadol hydrochloride (Amadol 50 mg mL^{-1}; ADWIA company, 10th of Ramadan city, Egypt) at a dose of 2 mg kg^{-1} IV. Group ıı; dogs were administered fentanyl citrate (50 μg mL^{-1} ;Janssen Pharmaceutica, Beerse, Belgium) at a dose of 5μg kg^{-1} IV.

2.3 Assessment of hematological and serum biochemical parameters

For assessment of these variables, a18 gauge intravenous catheter was inserted aseptically into left cephalic vein for blood samples collection. A total of 4 ml of blood was collected at each time point. To evaluate different hematological parameters including red blood cell count (RBCs), packed cell volume (PCV), hemoglobin concentration (Hgb), total leucocytic count (TLC), differential leucocytic counts and platelet count, a 1 ml of blood sample was transferred into EDTA vials and all parameters were determined using standard methods described by Feldman et al. (2000).

Clinical biochemical analyses including serum concentrations of total protein (TP), albumin, glucose, urea, creatinine and serum enzymatic activities of alanine transaminase (ALT) and aspartate transaminase (AST) were assessed using 3 ml of the collected blood sample which were transferred into 10 ml centrifuge tubes without anticoagulant and centrifuged at 3000 rpm for 5 minutes for serum separation. All of the studied biochemical parameters were determined by spectrophotometry using commercial colorimetric kits supplied by Biodiagnostic (Egypt).

2.4 Assessment of degree of analgesia

The degree of analgesia was scored using a scale ranging from 0 to 3 as previously described by Torad et al. (2009):

(0): Normal response to a painful stimulus

(1): Mild analgesia; depressed reaction to a painful stimulus

(2): Moderate analgesia; no response to skin pricks

(3): complete analgesia; no response to muscle pricks

All of the studied parameters were recorded at baseline (prior administration of analgesics), following administration of analgesic agents (0 time) (45 minutes following tramadol (Group I) and 7 minutes following fentanyl citrate (Group II), and for 1.5 hour later at 15 minutes interval (15, 30, 45, 60, 75 and 90 minutes).

2.5 Statistical analysis

All analyses were performed using the Statistical Software Package (SPSS Version 14.0). Data were analyzed using a paired- samples *t*-test to compare values of hematological and biochemical parameters obtained at each recording period with baseline values. Values obtained were expressed as mean ± S.E. The differences were considered to be significant when $P < 0.05$.

3. RESULTS

Data presented in Table 1&2 revealed that, red cell parameters did not show any significant changes in both groups following either tramadol or fentanyl administration. On contrary, assessment of total and differential leukocytic counts in Group I revealed a significant *($p< 0.05$)* decrease in total leukocytic and neutrophil counts from 15minutes up to 90 minutes recording time. On the other hand, a significant *($p< 0.05$)* increase in total leukocytic, neutrophil and lymphocyte counts were demonstrated at 15, 30, 75 and 90 minute periods in Group II. Eosinophil and monocyte counts did not exhibit statistically significant changes using both analgesics. Blood platelets were significantly higher in both groups compared to baseline data along the entire observation period except at 0 time in fentanyl group whereas insignificant increase was noticed.

In regard to serum biochemical parameters, both groups did not exhibit any significant changes in total protein, albumin and serum glucose levels. On contrary, in Group I, serum urea levels were significantly higher compared to baseline value from 0 time up to 75 minutes while, in Group II a significant *($p< 0.05$)* decrease was recorded at 15, 45 and 60 minutes. Furthermore, in Group II, a significant ($p< 0.05$) decrease in creatinine levels was demonstrated at 30 and 60 minutes with no significant changes being recorded in Group I. There was no difference between both analgesics considering their effects on creatinine clearance and serum enzymatic activities of ALT and AST whereas insignificant changes were recorded. All values are summarized in Table 3&4.

Considering the degree of analgesia obtained by both analgesic agents, in Group I, along the entire observation period, mild analgesia was recorded in four dogs with no detectable analgesia in remaining one while, in Group II, mild analgesia was recorded in four dogs with moderate analgesia being demonstrated in only one at the start of observation period (7 minutes post injection). At 15 and 30 minute periods, better analgesic score was recorded whereas moderate analgesia was observed in four dogs with mild analgesia in only one dog. At 45 minute recording time, four dogs exhibited mild analgesia with no analgesia in one dog followed by no detectable analgesia in any of the studied dogs in subsequent observation periods.

Table 1: Hematological parameters in dogs assigned to receive tramadol Hcl (Group I).

Parameter	Time (min.)							
	Baseline	Start time	15	30	45	60	75	90
RBCs ($x10^6/\mu l$)	5.87±0.26	5.94±0.09	5.77±0.31	5.64±0.02	5.50±0.35	5.59±0.41	5.67±0.24	5.53±0.33
PCV (%)	35.20±1.55	35.62±0.52	34.62±1.89	33.87±0.14	33±2.11	33.51±2.48	34.02±1.44	33.30±1.05
Hgb (g/dl)	11.74±0.52	11.88±0.18	11.54±0.63	11.29±0.04	11.002±0.70	11.17±0.83	11.35±0.48	11.05±0.49
TLC ($x10^3/\mu l$)	21.63±0.03	21.41±0.44	17.03±0.57*	16.08±0.32*	15.98±0.30*	14.88±0.44*	15.07±0.67*	17.13±0.09*
Neutrophil ($x10^3/\mu l$)	14.34±0.34	14.25±0.43	11.67±0.44*	11.17±0.10*	10.10±0.08*	9.08±0.06*	9.33±0.12*	11.78±0.44*
Eosinophil ($x10^3/\mu l$)	0.84±0.06	0.83±0.03	0.79±0.06	0.77±0.06	0.84±0.07	0.83±0.07	0.81±0.05	0.78±0.07
Lymphocyte ($x10^3/\mu l$)	4.83±0.40	4.72±0.37	3.03±0.58	2.66±0.23	3.43±0.19	3.39±0.09	3.46±0.16	3.06±0.07
Monocyte ($x10^3/\mu l$)	1.57±0.12	1.56±0.07	1.47±0.07	1.43±0.04	1.56±0.12	1.52±0.09	1.51±0.09	1.45±0.04
Platelet ($x10^3/\mu l$)	147.50±1.44	156.02±1.33*	158.09±0.63*	154.96±0.39*	152.55±0.33*	152.17±0.27*	161.97±0.42*	164.81±0.77*

RBCs, red blood cell count; PCV, packed cell volume; Hgb, hemoglobin concentration. All values are expressed as mean ± SE.
*Values are significantly different at that time point compared to baseline value. Significance is set at $p < 0.05$.

Table 2: Hematological parameters in dogs assigned to receive fentanyl citrate (Group II).

Parameter	Time (min.)							
	Baseline	Start time	15	30	45	60	75	90
RBCs ($x10^6/\mu l$)	6.19±0.35	5.94±0.47	5.79±0.58	5.84±0.13	6.03±0.10	6.03±0.06	6.07±0.09	6.13±0.21
PCV (%)	37.13±2.13	35.60±2.80	34.73±3.45	35.07±0.79	36.17±0.62	36.18±0.36	36.43±0.51	36.80±1.27
Hgb (g/dl)	12.38±0.71	11.86±0.93	11.58±1.15	11.69±0.26	12.06±0.21	12.06±0.12	12.14±0.17	12.27±0.42
TLC ($x10^3/\mu l$)	18.73±0.96	19.97±1.42	31.12±0.59*	27.24±0.34*	20.38±0.52	20.04±0.94	28.69±0.95*	28.55±0.33*
Neutrophil ($x10^3/\mu l$)	11.39±0.19	12.26±0.62	20.13±0.12*	17.56±0.89*	12.56±0.81	12.29±0.65	18.90±0.96*	18.74±0.89*
Eosinophil ($x10^3/\mu l$)	0.83±0.06	0.84±0.07	0.87±0.07	0.84±0.06	0.85±0.07	0.84±0.06	0.83±0.06	0.88±0.07
Lymphocyte ($x10^3/\mu l$)	4.90±0.51	5.26±0.32	8.44±0.56*	7.23±0.67*	5.33±0.34	5.29±0.35	7.34±0.59*	7.24±0.59*
Monocyte ($x10^3/\mu l$)	1.53±0.14	1.55±0.16	1.61±0.21	1.55±0.15	1.58±0.19	1.56±0.15	1.53±0.15	1.62±0.19
Platelet ($x10^3/\mu l$)	186.67±1.20	188.75±1.20	214.81±1.33*	199.39±1.06*	232.17±1.24*	227.25±0.80*	223.19±0.99*	201.23±1.51*

RBCs, red blood cell count; PCV, packed cell volume; Hgb, hemoglobin concentration. All values are expressed as mean ± SE. Values are significantly different at that time point compared to baseline value. Significance is set at $p < 0.05$.

Table 3: Serum biochemical parameters in dogs assigned to receive tramadol Hcl (Group I).

Parameter	Time (min.)							
	Baseline	Start time	15	30	45	60	75	90
TP (g/dl)	6.44±0.06	6.94±0.06	6.65±0.23	6.42±0.29	6.24±0.11	6.15±0.54	7.02±0.44	6.45±0.03
Albumin (g/dl)	3.05±0.17	2.83±0.03	2.76±0.11	3.08±0.14	3.20±0.11	3.16±0.01	3.62±0.53	3.40±0.01
Glucose (mg/dl)	86.86±1.08	86.30±0.56	84.81±1.67	86.08±1.82	83.87±1.72	82.80±1.03	85.62±0.96	86.53±0.75
Urea (mg/dl)	67.50±1.44	83.20±2.33*	81.20±2.02*	78.03±0.91*	78.16±0.86*	81.13±1.43*	83.99±0.14*	79.70±2.09
Creatinine (mg/dl)	0.68±0.01	0.68±0.02	0.69±0.02	0.68±0.02	0.69±0.01	0.69±0.02	0.69±0.01	0.68±0.01
ALT (U/L)	45.12±1.07	45.69±0.39	43.32±0.59	43.26±0.24	43.35±0.12	43.71±0.64	43.38±0.46	44.13±0.33
AST (U/L)	35.07±0.99	34.67±0.04	34.89±0.14	36.33±0.23	33.94±1.79	37.13±0.47	33.92±0.95	33.91±0.25

TP, Total protein; ALT, alanine transaminase; AST, aspartate transaminase. All values are expressed as mean ± SE.
*Values are significantly different at that time point compared to baseline value. Significance is set at $p < 0.05$.

Table 4: Serum biochemical parameters in dogs assigned to receive fentanyl citrate (Group II).

Parameter	Time (min.)							
	Baseline	Start time	15	30	45	60	75	90
TP (g/dl)	4.46±0.18	3.88±0.52	4.32±0.30	4.10±0.37	3.41±0.41	4.28±0.34	4.24±0.07	4.08±0.46
Albumin (g/dl)	2.89±0.50	2.84±0.49	2.74±0.14	2.59±0.35	2.70±0.17	2.71±0.20	2.62±0.37	2.81±0.48
Glucose (mg/dl)	73.20±0.89	78.25±0.45	76.06±0.86	75.61±0.87	75.17±2.61	77.68±2.74	75.44±0.99	75.33±1.20
Urea (mg/dl)	52.00±1.15	49.10±2.94	44.23±2.40*	47.12±1.60	44.76±0.44*	45.47±0.29*	47.95±3.14	51.43±0.96
Creatinine (mg/dl)	0.89±0.05	0.70±0.05	0.70±0.05	0.66±0.03*	0.70±0.05	0.64±0.02*	0.89±0.05	0.87±0.04
ALT (U/L)	47.82±1.14	47.42±2.11	48.66±0.93	46.83±2.27	45.87±2.16	47.58±2.25	47.05±1.86	46.53±1.47
AST (U/L)	34.79±0.37	36.24±1.18	37.07±0.94	34.95±0.60	35.38±0.03	35.63±0.74	35.26±0.89	34.89±0.28

TP, Total protein; ALT, alanine transaminase; AST, aspartate transaminase. All values are expressed as mean ± SE.
*Values are significantly different at that time point compared to baseline value. Significance is set at $p < 0.05$.

4. DISCUSSION

The aim of this study was to compare between the effect of tramadol Hcl and fentanyl citrate on some hematological and serum biochemical parameters in dogs.

Previous studies with tramadol have documented that, a dose of 2 mg kg^{-1} of intravenous tramadol provided sufficient post-operative analgesia in dogs undergoing either soft tissue (Mastrocinque and Fantoni, 2003) or orthopedic surgeries (Vettorato et al., 2010) based on these findings, In our work, tramadol was evaluated at a dose of 2 mg kg^{-1}. Furthermore, in Group ı, the first time point for assessment following tramadol was 45 minutes post injection depending on previous findings by Seddighi et al. (2009) whereas they demonstrated a significant reduction in sevoflurane MAC at 45 minutes following tramadol administration.

In present study, along the entire observation period following tramadol administration (Group ı), red cell parameters did not show any significant changes. These results are very similar to those previously reported by Costa et al. (2013) who recorded insignificant changes in these parameters between propofol-anesthetized dogs with or without tramadol.

A study by McMillan et al. (2008) have demonstrated in significant changes in blood biochemical parameters in dogs intravenously injected with tramadol at doses of 1, 2, and 4 mg/kg. In disagreement with these findings, our evaluation of serum biochemical parameters revealed statistically significant increase in serum urea levels following tramadol administration. Although the significant increase in serum urea, renal injury was not expected to be an inevitable consequence of the drug as serum creatinine concentrations did not show significant changes excluding the possibility of presence of renal dysfunction. This was further supported by the results of creatinine clearance which showed no significant alterations after tramadol administration. These results is compatible with previous findings by Kongara et al. (2009) whereas they demonstrated in significant changes in glomerular filtration rates in halothane anesthetized dogs following tramadol administration.

In Group ıı, fentanyl was assessed at a dose of 5µg kg^{-1} according to Psatha et al. (2011) who previously found that, 5µg kg^{-1} of fentanyl combined with diazepam 0.2 mg kg^{-1} ± propofol 1–2 mg kg^{-1} was effective for induction of anesthesia in dogs that are a poor anesthetic risk. Additionally, in this group, the start time for fentanyl to be evaluated was 7 minutes post injection according to Hall et al. (2001) as they reported that, fentanyl becomes effective within 4-7minutes following I.V injection in dogs.

Regarding the effect of fentanyl on hemogram, a significant increase in total leukocytic, neutrophil and lymphocyte counts was recorded which agreed with a previous work by Fox (2014) who observed that, administration of transdermal fentanyl solution (50mg/ml) in dogs was associated with increased white blood cells.

Biochemical changes in Group ıı, included a significant decrease in serum urea levels at 15, 45 and 60 minutes and in serum creatinine levels at 30 and 60 minutes. These findings could be explained in terms of the previously reported fentanyl associated hypertension (Hendrix *et al.* 1995) which possibly increased renal blood flow with subsequent increase in glomerular filtration rate. No changes were demonstrated in creatinine clearance. These findings disagreed with those reported by Castiglia et al. (1997) who declared that creatinine clearance was significantly decreased by fentanyl administration. However, this discrepancy between the two studies could be attributed to the higher dose of fentanyl (0.05 mg/kg) used by Castiglia et al. (1997) compared with the dose (5µg/kg) evaluated in our work.

In the present study, tramadol administration induced only limited analgesia (mild analgesia) in treated dogs. Consistently, Mastrocinque and Fantoni (2003) clarified that, if M1 production is limited in other breeds of dogs similar to that demonstrated by Wu et al. (2001) in beagles, this may make tramadol a less effective analgesic in dogs than in people. On contrary, greater degree of analgesia was obtained following fentanyl administration which evidenced by absence of response to skin pricks in four of the studied dogs at 15 and 30 minute observation periods which could be explained in terms of documented analgesic potency of such drug which possess an

analgesic potency that is 75 to 125 times the potency of morphine. (Hellyer et al., 2001).

5. CONCLUSION

This study demonstrated that, administration of either tramadol or fentanyl in dogs was not associated with significant alteration in red cell parameters. On contrary, both analgesics feasibly affect leukogarm with better influence for fentanyl compared to tramadol. Additionally, both of them did not show any negative impact on platelet counts. Besides, from all serum biochemical parameters, urea and creatinine levels were the only that exhibited significant changes demonstrating significant decrease in fentanyl group with significant increment in urea levels in tramadol group at some time periods. On the basis of these findings, fentanyl might be superior to tramadol regarding some of the studied hematobiochemical parameters in dogs. Assessment of degree of analgesia, ascertain also the analgesic efficacy of fentanyl over tramadol. Consequently, it can be concluded that, fentanyl at the dosage used in this study can be recommended as a valuable and safe opioid for providing perioperative analgesia in canine patients.

6. ACKNOWLEDGEMENTS

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