Evaluation of haematological and biochemical changes after short term tramadol usage in healthy dogs

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Abstract:

BACKGROUND: Tramadol is a synthetic, centrally acting opioid analgesic that has the best analgesic efficacy without excessive sedation and significant side effects in the postoperative pain relief in dogs. **OBJECTIVES:** In this study, hematological and biochemical changes due to short usage of tramadol were assessed in clinically healthy dogs. **METHODS:** For this purpose, eighteen male mongrel dogs aged 14 to 22 months were used in three equal groups. In the first and second groups respectively (2 and 5 mg/kg) intramuscular tramadol and in control group distillate water was given once a day for five consecutive days. Complete cell blood count (CBC) and biochemical evaluation were done to measure aspartate amino-transferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinin (Cr), and blood urea nitrogen (BUN) levels, before the intervention (day 0) and on days 6 and 13, post-treatment. **RESULTS:** Thirteen days post treatment, Red blood cell (RBC) and white blood cell (WBC) count and ALT, AST, ALP, Cr, BUN and packed cell volume (PCV) level was measured as 6.75±0.03, 3.86±0.13, 40.00±7.98, 43.67±8.62, 57.00±17.03, 0.90±0.27, 25.00±5.48 and 40.13±2.88 respectively which showed that short-term injection of even high doses of tramadol creates no significant change on hematological, liver, and kidney parameters in dogs. **CONCLUSIONS:** The present study suggests that tramadol could be a safe postoperative analgesic for control of acute pain in dogs referred for routine surgical procedures.

Introduction

The recognition of animal pain as a medical entity and ethical problem has attracted increasing scientific attention, leading to better animal welfare laws. Tramadol, a synthetic racemic mixture of the 4-phenyl-piperidine analogue of codeine, has received widespread acceptance in human medicine since it was first introduced in 1977 in Germany (Schenck and Arend, 1978; Osterloh et al., 1978; Scott and Perry, 2000). Tramadol plays an important role in the management of pain with its dual mechanism of action (opioid agonist; weak noradrenaline and serotonin reuptake inhibitor). Besides its proven clinical efficacy, tramadol is a safe drug with no respiratory depression, cardiovascular side effects, drug abuse, and minor clinical relevance of dependency, unlike some other opioids (Quang -

Cantagrel et al., 2000). Elimination is primarily by the hepatic route (metabolism by CYP2D6 to an active metabolite and by CYP3A4 and CYP2B6) and partly by the renal route (up to 30% of dose). Elimination half-lives of the active agents range between 4.5 and 9.5 hours, and the total plasma clearance of tramadol is moderately high (600 ml/min) (Klotz, 2003). The metabolism of tramadol has been investigated in a number of animal species (rats, mice, Syrian hamsters, guinea pigs, rabbits and dogs) as well as in humans (Lintz et al., 1981; KuKanich and Papich, 2004). The central role of liver and kidney in drug metabolism predisposes them to toxic injury. Tramadol is converted in the liver to O-desmethyl-tramadol, which is an active substance and 2 to 4 times more potent than tramadol (Wu et al., 2001; Tao et al., 2002). Furthermore, biotransformation results in inactive metabolites, which are excreted by kidneys (Lee et al., 1993; Matthiessen et al., 1998, Atici et al., 2005). Likewise, if kidney or liver function is severely impaired, some dosage reduction (approximately by 50%) or extension of the dosage interval should be considered (Klotz, 2003). The efficacy of tramadol in pain relief in small animal medicine was confirmed in previous studies (Cagnardi et al., 2011; Vettorato et al., 2010). However, in this study, haematological and biochemical changes in liver and kidneys due to short usage of tramadol were assessed in healthy dogs.

Materials and Methods

Animals: In this study, eighteen healthy male mongrel dogs were used, with body weight ranging between 20 to 30 kg, and ages between 14 and 22 months. The dogs were considered healthy based on physical examination, complete blood count, serum biochemistry, and urine analysis before the initiation of the study. All animals were kept in an approved animal care facility in separate cages with ad libitum access to food and water. They were divided to three equal (two treatments and one control) groups.

Drug administration: Two treatment groups were given intramuscular tramadol (Aboraihan company, Iran), once a day 2 and 5 mg/kg, respectively, and the control group was given distilled water for five consecutive days.

Blood sampling protocol: Blood samples were taken from the brachiocephalus vein from the control and treatment groups, prior to the experiment (day 0), at the end of treatment period (day 6), and one week later (day 13). Five-milliliter (5mL) blood samples were divided in two tubes, 1 mL used with anticoagulant, ethylenediamine tetra-acetic acid (EDTA) for haematological evaluation and 4 mL without anticoagulant, for serum collection and biochemical assay.

Haematological studies: Complete blood counts were performed by cell counter instrument (EXW Shenzhen, China) for all dogs.

Biochemical studies: Serum samples were separated by centrifugation for measurement of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and creatinine level using an autoanalyzer (Autolab, AMS -18A, China) and commercial kits (Mans company, Iran) according to the manufacturer's instructions.

Statistical analysis: Statistical analyses were performed using repeated-measures analysis of variance. For WBC and RBC, analysis was done on log 10 of measures. Data were presented as mean ± SD and $p<0.05$ was considered statistically significant. All calculations were made using SPSS version 18.

Results

There were no significant differences in the studied parameters between different groups. Although significant differences were seen in hepatic enzymes level during different times in some animals in treatment groups, all kidney and liver enzymes and haematological parameters (mean levels) were in the normal range in the studied dogs on days 6 and 13 post-treatment in two treatment groups, suggesting that tramadol is a safe post-operative analgesic for control of acute pain in dogs (Table 1).

Discussion

Opioids are used in veterinary and human medicine. It has been proven that liver and kidney are responsible for the metabolism and excretion of all opioids (coughtvie et al.,1989; Milne et al., 1997; Bannwarth, 1999). Based on author's knowledge,

Table1. Mean± SD level of haematological and biochemical parameters in studied dogs. (*) Before intervention (Day 0). (**) Day 6. (***) Day 13.

Parameter	Control	Tramadol(2mg/kg)	Tramadol (5 mg/kg)
	Mean±SD	Mean±SD	Mean±SD
Log-RBC/µL (Red Blood Cell)			
T0(*)	6.74±0.03	6.75±0.03	6.75±0.03
T1(**)	6.74±0.03	6.73±0.03	6.92±0.41
T2(***)	6.76±0.03	6.92±0.40	6.75±0.03
Log-WBC/µL (White Blood Cell)			
T0	3.97±0.07	3.96±0.06	3.97±0.08
T1	3.87±0.06	3.90±0.06	3.94±0.07
T2	3.92±0.07	3.92±0.04	3.86±0.13
ALT (IU/l)			
T0	23.50±5.92	25.50±7.39	28.33±4.63
T1	34.67±9.20	37.00±6.07	38.00±13.47
T2	34.00±10.37	39.17±8.57	40.00±7.98
AST (IU/l)			
T0	26.17±7.90	32.00±8.76	38.33±9.85
T1	28.67±15.59	35.67±6.89	42.67±9.56
T2	28.17±15.63	36.33±9.73	43.67±8.62
ALP(IU/l)			
T0	57.67±17.44	57.83±16.65	44.83±14.27
T1	63.50±18.27	61.33±12.74	54.50±17.48
T2	66.67±18.62	71.83±17.11	57.00±17.03
Cr(IU/l)			
T0	0.83±0.29	0.75±0.22	0.57±0.12
T1	0.88±0.29	1.00±0.28	0.72±0.28
T2	0.91±0.28	0.97±0.24	0.90±0.27
BUN (mg/dl)			
T0	21.50±6.31	19.33±5.78	18.67±5.56
T1	25.33±7.94	34.50±6.66	24.00±6.63
T2	23.83±7.17	25.83±8.64	25.00±5.48
PCV (%)Packed Cell Volume			
T0	40.50±1.97	40.50±2.67	38.83±3.13
T1	41.35±2.59	38.15±4.30	39.13±2.68
T2	39.67±1.97	42.58±2.88	40.13±2.88

there is no investigation about the side effects of short or long term tramadol administration on hematological and biochemical factors in dogs, whereas results of the present study showed that short term tramadol administration to dogs does not induce any significant hematological, renal and hepatic disorders.

Hepatotoxic effects of both morphine and tramadol were confirmed after long-term administration in rats; however, the toxic effects of tramadol were less severe compared to morphine. On the other hand, no significant changes were seen in BUN and creatinin levels after chronic usage of tramadol, indicating that tramadol may be a safer drug in terms of renal side effects compared to morphine (Atici et al., 2005). Renal damage like focal corticomedullary mineralization, focal regeneration in tubular epithelium, and mineral crystal deposition in intertubular region in kidneys has been reported after long-term use of morphine like agent, levo-alpha acetyl methadol hydrochloride (Borzelleca et al., 1994). Nevertheless, tramadol caused minimal histopathological changes in kidneys limited only to tubular cells in rats (Atici et al., 2005). A significant increase in the level of ALT, which has been reported among long term heroin users, were also indicated after long term usage of tramadol (Panchenko et al., 1999; Atici et al., 2005). In another study that was performed by Habibian-Dehkordi et al. (2010), short term intravenous administration of tramadol had no effect on ALT, AST, and ALP levels in sheep, which is in agreement with our study. On the other hand, no significant changes were observed in BUN and Cr levels in blood serum by these researchers, the same as what we found in the present study (Habinian-Dehkordi et al., 2010).

Total number of WBC did not show any significant changes during present experiment, which is against Tsai's (2001) findings which showed that tramadol administration causes an increase in number of lymphocytes in rats. Other M opioid agonists like morphine were reported to cause decrease in the number of lymphocytes (Tsai and Won, 2001).

The number of blood RBC and packed cell volume were the other hematological parameters that were considered in normal range, and tramadol did not affect them in our study. In a study by Verde et al. (2003), it was shown that Hb, hematocrit, RBC, and WBC counts in blood samples of opiate addicts of both sexes were higher than those levels found in control groups. On the contrary, a significant decrease in RBC count and PCV was indicated after short-term tramadol administration in sheep (Habibian-Dehcordi et al., 2010; Verde et al., 2003).

In conclusion, results of the present study showed that short-term injection of various doses of tramadol has no significant effect on hematological, liver, and kidney parameters in dogs, suggesting that tramadol may be an effective postoperative analgesic for control of acute pain in dogs referred for routine surgical procedures. Further investigation about the side effects of long term tramadol administration in dogs must be performed.

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مجله طب دامی ایران، ۱۳۹۳، دوره ۸، شماره ۱، ۴۵-۴۱

ارزیابی تغییرات هماتولوژیکی و بیوشیمیایی خون پس از تجویز کوتاه مدت ترامادول در سگ های سالم

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چکیده

زمینه مطالعه: ترامادول یک مخدر فعال مرکزی و سنتتیک است که بهترین اثر گذاری را بدون ایجاد آرام بخشی مفرط و عوارض جانبی قابل توجه در سگ ها داراست. **هدف:** در این مطالعه تغییرات بیوشیمیایی و هماتولوژیکی متعاقب تجویز کوتاه مدت ترامادول در سگ های سالم تعیین شد. **روش کار:** برای این منظور ۱۸ قلاده سگ نر دورگه که سنی بین ۲۲-۱۴ ماه داشتند در ۳ گروه مساوی مورد استفاده قرار گرفتند. در گروه اول و دوم به ترتیب ۲kg/gm و ۵ ترامادول به صورت داخل عضلانی و در گروه کنترل، آب مقطر روزی یک بار به مدت ۳ روز متوالی تجویز شد. شمارش کلی سلول های خونی و ارزیابی بیوشیمیایی جهت اندازه گیری سطوح آسپارتات آمینو ترانسفراز (AST)، آلانین آمینوترانسفراز (ALT)، لاکتات دهیدروژناز (LDH)، کراتینین و نیتروژن اوره خون (BU)N، قبل از تجویز (روز صفر)، روز ۶ و روز ۱۳ پس از درمان انجام گرفت. **نتایج:** نتایج نشان داد که تزریق کوتاه مدت ترامادول با دوزهای متفاوت تأثیر معنی داری بر فاکتورهای هماتولوژیک، کبدی و کلیوی در سگ ها ندارد. **نتیجه گیری نهایی:** این مطالعه پیشنهاد می کند که ترامادول می تواند به عنوان به یک داروی تخفیف دهنده مناسب درد در کنترل درد حاد متعاقب جراحی های معمول در سگ استفاده شود.

واژه های کلیدی: سگ، کلیه، کبد، ترامادول

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