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RESEARCH ARTICLE

# Effects of Tramadol on Electrocardiogram, Mean Electrical Axis and Respiration in Kagani Goats (*Capra hircus*)

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**ABSTRACT**

The effects of tramadol on electrocardiogram (ECG), mean electrical axis and respiratory rates were studied in adult kagani goats after intramuscular administration of tramadol at 1 mg/kg b.wt as a prelude to its clinical use as an analgesic in veterinary practice. The ECG was monitored by standard bipolar leads and discernible electrocardiographic features were observed in lead II. The normal electrocardiographic parameters in healthy goats were; P-wave (0.04 ± 0.005 mV, 48 ± 4.29 ms), QRS complex (0.38 ± 0.037 mV, 84 ± 2.86 ms), T-wave (0.11 ± 0.005 mV, 76 ± 1.28 ms), PR, ST, QT intervals were 152 ± 5.72, 280 ± 7.29, 368 ± 18.60 ms, respectively. These parameters were not significantly different in goats up to 3h post treatment. Except significant reduction in T-wave amplitude ($p$<0.05) at 0.5h, no other significant change was observed. Reduction in T-wave indicates early re-polarization phenomenon and is indicative of some transient cardio-acceleratory effect of the drug. The mean electrical axis ($56.74^0 \pm 0.6^0$) before treatment didn't show significant differences up to 3h of post-treatment. The rate of respiration prior to treatment was observed 19.6 ± 2.57min$^{-1}$ and administration of tramadol didn't produce any significant change on respiration up to 3h post treatment.

**Keywords:** *Tramadol, Electrocardiogram, Mean electrical axis, Respiration, Kagani goats*

Tramadol, a codeine analog, is a centrally acting synthetic analgesic and the drug owes its analgesic action to its weak opioid (μ) receptor agonist activity and inhibition of uptake of nor-epinephrine and serotonin. Tramadol is as effective as meperidine in the amelioration of labor pain and cause less respiratory depression in humans. The drug is also being considered to be a better alternative in comparison to other opioid analgesics in humans because of high analgesic potency and minimal respiratory depression at analgesic doses [1]. The analgesic activity of tramadol is due to both parent as well as its O-demethylated metabolite and this metabolite is 4-6 times more potent than the parent [2]. Tramadol is supplied as a racemic mixture, which is more effective than either of the enantiomer alone. The (+) enantiomer binds to the μ receptor and inhibit serotonin uptake whereas (-) enantiomer inhibit nor-epinephrine uptake and blocks $\alpha_2$ receptors [3]. *In vitro* and *in vivo* studies also suggested that only (+)ve enantiomer of tramadol-induce vasodilatation at high doses indicating that tramadol can be used safely at therapeutic dose [4]. The vasodilation induced by tramadol is due to both nitric oxide production from endothelium and a direct effect on smooth muscle mediated via interaction with the μ receptors [4, 5].

Electrocardiographic studies are infrequently reported in animals [6, 7]. The electrocardiographic parameters have greatest value in recognizing and diagnosing arrhythmias in animals [8]. Variability in normal duration and amplitude of different electrocardiographic parameters are useful in evaluating the side effects of commonly used therapeutic drugs [9]. Mean electrical axis values (MEA) determine the site, size and direction of the conduction system of the heart, which is individual or a breed characteristic [10]. Studies on effects of tramadol on electrocardiographic parameters, mean electrical axis and respiration in goats are scarce. The study was pursued with the objective to determine different electrocardiographic parameters in normal goats and the effect of tramadol on these parameters at analgesic dose.

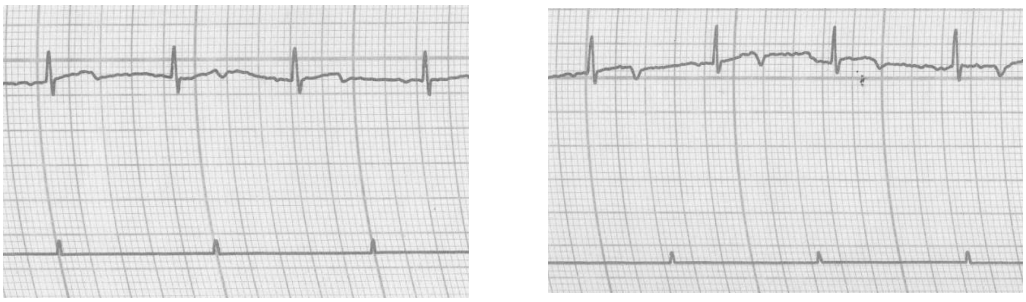

**Fig 1 a.** Electrocardiograms of Lead II of goat before (A) and after 0.5h (B) tramadol treatment, using physiograph Medicaid, Chandigah, India. Sensitivity 500µv and chart speed, 2.5 cm per second.

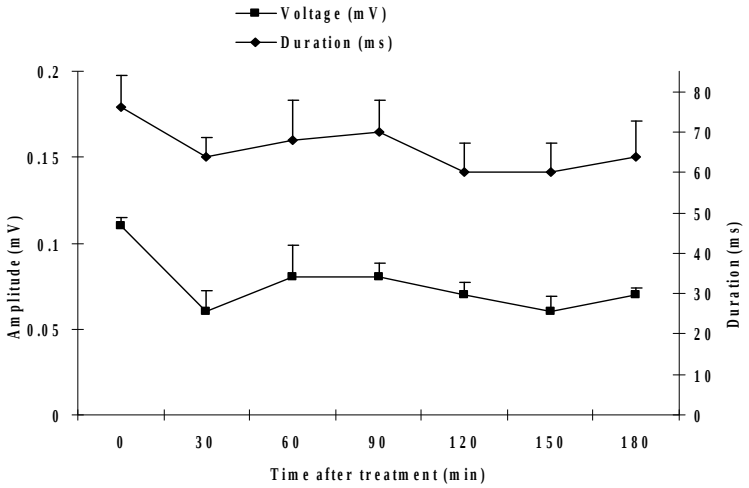


**Fig 1 b.** Graphical representation amplitude (mV) and duration (ms) of T-wave before and after administration of tramadol

## MATERIALS AND METHODS

Healthy kagani goats (*Capra hircus*) of either sex aged 2-3 years were selected for the study. The animals were housed in the animal shed of Faculty of Veterinary Sciences, at R.S. Pura, Jammu (INDIA). All animals were maintained under standard condition of feeding and management. The animals were fed green fodder and concentrates at standard rates and free access to water. The studies were conducted in the month April-June when ambient temperature varied in between 35 - 400C. During recording of electrocardiogram (ECG) goats were made to stand on wooden plane. Needle electrodes were inserted subcutaneously proximal to the olecranon on the caudal aspect of the right and left forelegs for the right and left arm wires, respectively and in the external aspect of the stifle joint of the right and left leg wires, respectively [11]. The three standard bipolar limb leads (I, II, and III) and augmented unipolar limb leads (aVR, aVL and aVF) were recorded on paper using a three channel physiograph (Medicaid, Chandigah, India). A commercial human pharmaceutical preparation of Tramadol (Cadilla Health Care, Ahmadabad, India) was administered intramuscularly at the dose rate of 1mg kg-1body wt. Recording of ECG parameters were done before and after the administration of drug. Most of the opioids like pentazocine provide effective analgesia for (1-6 h) when they are used in a dose range of 0.4-2mg kg-1 intramuscularly [12]. Therefore, a dose of 1mg kg-1 body wt. was selected. The reported half life of drug in dogs is 0.80±0.12h [2]. Therefore the recording of ECG parameters and respiration were done at different pre-determined time intervals up to 3h of post administration. The mean electrical axis was calculated by the method of described by Dragutin and co-workers in 1999 [13]. The results obtained were analyzed statistically using paired t-test between mean obtained before and after treatment [14].

## RESULTS AND DISCUSSION

Present investigation employed human technique of Einthoven's triangle in ventral plane quite successfully in goats in standing position [15]. It was observed that various components were quite discernible in unipolar and bi-polar limb leads. Therefore, comparisons were based on lead II electrocardiogram. Table 1 depicts the recorded values during the experiments on goats on duration and amplitude of P wave, duration of the QRS complex, mean electrical axis, duration of PR and QT intervals, S-T segment and respiration before and at different predetermined time intervals post administration of tramadol.

**Table 1.** Comparative electrocardiographic parameter and respiration in Kagani goat and effect of Tramadol hydrochloride @ 1mg.kg-1 intramuscular administration

| Parameter | | Control | After Treatment (min.) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 30 | 60 | 90 | 120 | 150 | 180 |
| P - wave | Voltage (mV) | 0.04±0.005 | 0.06±0.007 | 0.045±0.003 | 0.045±0.007 | 0.04±0.005 | 0.04±0.005 | 0.04±0.005 |
| | Duration (ms) | 48±4.29 | 40±1.78 | 44±6.44 | 40±3.57 | 40±1.78 | 44±2.86 | 40±3.57 |
| QRS complex | Voltage (mV) | 0.38±0.037 | 0.40±0.047 | 0.39±0.029 | 0.37±0.031 | 0.375±0.049 | 0.37±0.0375 | 0.37±0.044 |
| | Duration (ms) | 84±2.86 | 80±1.78 | 76±2.86 | 88±5.72 | 82±3.22 | 82±3.22 | 82±3.22 |
| T - wave | Voltage (mV) | 0.11±0.005 | 0.06±0.012* | 0.09±0.019 | 0.08±0.008 | 0.07±0.007 | 0.06±0.009 | 0.07±0.004 |
| | Duration (ms) | 76±7.85 | 64±1.76 | 68±10.0 | 72±7.87 | 60±7.15 | 60±715 | 64±8.58 |
| PR interval (ms) | | 152±5.72 | 176±8.58 | 160±7.15 | 176±8.58 | 168±5.72 | 168±11.4 | 192±5.72 |
| ST interval (ms) | | 280±7.29 | 292±11.4 | 280±7.15 | 284±4.65 | 264±8.58 | 284±2.86 | 272±5.72 |
| QT interval (ms) | | 368±18.60 | 360±7.15 | 360±7.15 | 364±4.65 | 344±8.58 | 352±5.72 | 344±8.58 |
| Mean Electrical Axis | | 56.74±3.6 | 55.52±2.64 | 57.1±4.6 | 56.9±2.46 | 57.3±4.4 | 56.36±3.02 | 56.52±4.78 |
| Respiration ($min^{-1}$) | | 19.6±2.57 | 18.6±3.57 | 17±1.71 | 19.8±2.28 | 20.2±3.50 | 20±3.35 | 20±4.17 |

Values are expressed as mean ± S.E. of recording six adult animals
Mean treatment values are different from the mean control values at 5% ($p$<0.05)

In present study prior to treatment the amplitude and duration of P-wave signifying atrial depolarization were 0.04±0.005 mV and 48±4.29 ms, respectively which is comparable with kids and lambs [5] but lesser than 0.229±0.06 mV reported for dogs [16]. The administration of tramadol didn't produce significant changes in the amplitude and duration of P-wave up to 3 h post administration.

Control values of ventricular depolarization represented by amplitude of QRS complex is 0.38±0.037 mV which is higher than the reported values of (0.17±0.086mV) in kids but is comparable to cats (0.427±0.25mV) [5, 17]. The higher QRS amplitude in goats in the present study indicates higher systolic pressure [17]. In the present study duration of QRS complex was 84±2.86ms is lower than in kids (93±7ms) but higher than reported values in dogs (54±0.01ms), cats (32±0.007ms) and llamas (50.0±8.00ms) [16,17,18]. Administration of tramadol didn't effect duration and amplitude of QRS complex. Tilley, 1985 has suggested that longer QRS complex duration to be a resultant of a heart block or enlargement of either of ventricle or both ventricles.

Significant reduction in T-wave amplitude (0.06±0.009mV) at 0.5h post administration was observed as compared to control (0.11±0.005mV) and representative recording is shown in fig.1a and b. However, no such significant reduction in duration of T-wave was observed. The decrease prominence T-wave indicate re-polarization phenomenon of the ventricles particularly basal part is rather rapid and the next cardiac cycle begins quickly thereby indicative of cardio accelerator effect of tramadol. The control duration of ST and QT intervals are higher than the reported values of kids 220±12ms, 313±13ms, but comparable with llamas 230±46, 360±60ms respectively [7, 18]. However no significant change was observed in these intervals up to 3h of post treatment compared to pretreatment values. Determination of electrical axis of heart is an important aid for understanding deviation of impulse conduction in the heart and can help in diagnosis of pathological conditions of heart. In the present study tramadol didn't significantly affect the mean electrical axis values ($56.74^0 \pm 0.6^0$) in goats. The respiration rates reported for goats are in the range of 12-25 $min^{-1}$ [19] and tramadol didn't affect significantly respiration rates (19.6±2.57 $min^{-1}$). Conversely opiate substitutes like, pentazocine causes significant reduction in respiration in kids [7]. Finding also suggested that tramadol also provides a cardio-protective effect against myocardial ischemia-reperfusion in isolated rat heart [20].

From the results it can be concluded that at the dose rate 1mg $kg^{-1}$ in goats, tramadol is a safe analgesic due to its mild and transient effect on ECG events without effecting respiration.

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