ECG CHANGES IN DOGS SEDATED WITH DEXMEDETOMIDINE AND MIDAZOLAM-DEXMEDETOMIDINE COMBINATION

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The present study was conducted in clinically healthy dogs to investigate the electrocardiographic changes produced by dexmedetomidine, an alpha-2 agonist and its combination with midazolam. Electrocardiographic changes like sinus arrhythmia, first degree heart block and wandering pace maker were recorded in both groups. P wave duration was variable whereas amplitude decreased in both groups. Dexmedetomidine induced bradycardia caused increased in PR interval in both groups. QRS complex duration and amplitude increased in both groups. T wave complex was also increased but its morphology is not of any significant value in small animals. Addition of midazolam did not cause considerable adverse effects on ECG changes induced by dexmedetomidine in dogs.

Key words: DExmedetomidine, dogs, electrocardiography, Midazolam.

Introduction
Dexmedetomidine, the latest alpha-2 agonist, is the active optical isomer of racemate medetomidine, which is used as a sedative and preanaesthetic in veterinary practice. Studies have revealed that dexmedetomidine may offer sedative and analgesic benefits over medetomidine. In dogs, dexmedetomidine produces dose dependent sedation and analgesia and the intensity of these effects is similar to that produced by twice the dose of medetomidine (Kuusela et al., 2000). Dexmedetomidine; like other alpha-2 agonists, acts on the presynaptic alpha-2 receptors on various neuronal and non-neuronal sites and inhibits noradrenaline release from sympathetic nerve terminals. The alpha-2 adrenergic receptor mediates its effects by activating G-proteins, which modulate cellular activity by signaling a second messenger system, leading to the inhibition of adenylate cyclase which in turn results in decreased formation of 3, 5-cyclic adenosine monophosphate (cAMP) (Cotecchia et al., 1990, Birnbaumer et al., 1990). All these events lead to efflux of K+ through an activated channel causing hyperpolarization and suppression of neuronal firing. Ca++ entry into the nerve terminals is also reduced by alpha-2 adrenoreceptor activation, which may be responsible for its inhibitory effects on secretion of neurotransmitters (Hayashi and Maze, 1993, Khan et al., 1999).

Administration of alpha-2 agonists is associated with a number of electrocardiographic changes. Sinus bradyarrhythmia, AV block, sinus pause are not uncommon (Lemke, 2004). Benzodiazepines like midazolam have been used with dexmedetomidine to enhance muscle relaxation and sedation (Ahmad et al., 2011). The benefits of a combination of a benzodiazepine and an alpha-2 agonist lie not only in induction of profound muscle relaxation and sedation but also in the ability to selectively counteract CNS depression with receptor specific antagonist (Tranquilli et al., 1990). Electrocardiographic profile is an important indicator of functional and physiological status of the heart, however, it has not been studied sufficiently when combination of dexmedetomidine and midazolam was used. The present study was therefore conducted to evaluate the effect of dexmedetomidine and its combination with midazolam on electrocardiographic parameters in dogs.

Materials and Methods
The study was conducted in the Division of Surgery and Referral Veterinary Polyclinic, Indian Veterinary Research Institute, Izatnagar.

Animals
Client owned, mixed breed dogs of either sex, with a average weight of 17 kg and average age of 2 years, presented to the Referral Veterinary Polyclinic for minor therapeutic and diagnostic procedures like radiography, clinical examination, abscess drainage, wound dressing etc. were made the subjects for the study. An informed consnt was obtained from the animal owners before
conducting the experiment. The study was conducted on 8 apparently healthy adult dogs, divided randomly into two groups of four animals each. The groups of animals were designated as group A and group B.

In group A, dexmedetomidine 20 μg/kg, while in group B, dexmedetomidine (20 μg/kg) along with midazolam (0.2 mg/kg) was administered intramuscularly. The animals were restrained properly and spirit swab was used to disinfect the skin over the anterior thigh muscles (biceps femoris) and the drugs were administered using disposable syringes.

The animals were restrained on a nonconductive surface to eliminate electrical interference. The animals were kept in right lateral recumbency with fore and hind limbs perpendicular to the long axis of the body. Clip electrodes were attached directly to the animal’s skin. The right arm (RA) and left arm (LA) electrodes were attached proximal to olecranon on the caudal aspect of the respective leg. The right foot (RF) and left foot (LF) electrode clips were attached over the patellar ligament on the anterior aspect of the respective hindlimb. The skin and electrodes were moistened with 70% alcohol before application of ECG electrodes. Electrocardiographic recordings at 1 mV and 50 mm/s paper speed were made at 0, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min intervals using ECG Machine, Cardioart 6108T, (BPL Limited, India) on a lead II system.

**Statistical Analysis**

Paired “t” test was used to compare the mean values between the two groups and also at different intervals with their base values in each group (Snedecor and Cochran, 1980).

**Results and Discussion**

Values of various ECG parameters recorded in two groups at different intervals are presented in table 1. Some of the important changes are also depicted in Fig. 1. Normal sinus rhythm was present in all the dogs at the baseline. After drug administration sinus bradyarrhythmia was observed in all the animals of group A. In group A, sinus block was observed in one animal. In group B, along with sinus arrhythmia, first degree heart block and wandering pacemaker within SA node were seen.

Administration of alpha-2 agonists is associated with a number of electrocardiographic changes. Sinus bradyarrhythmia, AV block, sinus pause are not uncommon (Lemke, 2004). Accentuated sinus arrhythmia with sinus pauses along with occasional first degree A-V block have been

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![Sinus arrhythmia at 30 min](image1)

![Sinus arrest with first degree heart block at 45 min](image2)

![Sinus arrhythmia at 120 min](image3)

Fig. 1: ECG tracings showing some of the ECG changes recorded in group A
reported following dexmedetomidine administration in dogs (Kuusela et al., 2000). Second degree AV block with wandering pacemaker and escape beats were detected in some dogs in which medetomidine-hydromorphone combination was used (Kuo and Keegan, 2004) whereas sinus arrhythmia with second degree heart block was seen after administration of combination of medetomidine-ketamine (Ko et al., 2000).

Table 1: Mean ±SE of various ECG parameters recorded in different groups at different interval

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>0</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
<th>105</th>
<th>120</th>
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<tr>
<td>P-wave duration</td>
<td>A</td>
<td>0.040 ±0.000</td>
<td>0.038 ±0.003</td>
<td>0.037 ±0.002</td>
<td>0.038 ±0.001</td>
<td>0.038 ±0.002</td>
<td>0.040 ±0.000</td>
<td>0.042 ±0.002</td>
<td>0.043 ±0.002</td>
<td>0.041 ±0.002</td>
<td>0.039 ±0.001</td>
<td>0.040 ±0.000</td>
</tr>
<tr>
<td>B</td>
<td>0.042 ±0.003</td>
<td>0.045b ±0.004</td>
<td>0.044 ±0.005</td>
<td>0.046 ±0.003</td>
<td>0.042 ±0.004</td>
<td>0.034 ±0.004</td>
<td>0.043 ±0.002</td>
<td>0.035 ±0.005</td>
<td>0.042 ±0.002</td>
<td>0.032 ±0.004</td>
<td>0.036 ±0.003</td>
<td></td>
</tr>
<tr>
<td>P-wave amplitude</td>
<td>A</td>
<td>0.170 ±0.013</td>
<td>0.150* ±0.160</td>
<td>0.160 ±0.027</td>
<td>0.130* ±0.001</td>
<td>0.120* ±0.011</td>
<td>0.140* ±0.012</td>
<td>0.120* ±0.018</td>
<td>0.150* ±0.020</td>
<td>0.140* ±0.023</td>
<td>0.140* ±0.022</td>
<td>0.170* ±0.033</td>
</tr>
<tr>
<td>B</td>
<td>0.130 ±0.016</td>
<td>0.098b ±0.012</td>
<td>0.090 ±0.020</td>
<td>0.091 ±0.023</td>
<td>0.095 ±0.023</td>
<td>0.088b ±0.020</td>
<td>0.082 ±0.020</td>
<td>0.076b ±0.020</td>
<td>0.064b ±0.020</td>
<td>0.060b ±0.020</td>
<td>0.060b ±0.012</td>
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<td>P-R interval</td>
<td>A</td>
<td>0.093 ±0.004</td>
<td>0.11** ±0.006</td>
<td>0.098 ±0.010</td>
<td>0.11** ±0.005</td>
<td>7</td>
<td>0.11** ±0.006</td>
<td>0.12** ±0.006</td>
<td>0.12** ±0.005</td>
<td>0.11** ±0.005</td>
<td>0.11** ±0.005</td>
<td>0.12** ±0.006</td>
</tr>
<tr>
<td>B</td>
<td>0.09 ±0.003</td>
<td>0.14** ±0.006</td>
<td>0.14** ±0.004</td>
<td>0.09** ±0.020</td>
<td>0.14** ±0.008</td>
<td>0.15** ±0.008</td>
<td>0.14** ±0.010</td>
<td>0.12** ±0.010</td>
<td>0.15** ±0.009</td>
<td>0.15** ±0.008</td>
<td>0.15** ±0.008</td>
<td></td>
</tr>
<tr>
<td>QRS duration</td>
<td>A</td>
<td>0.054 ±0.000</td>
<td>0.060 ±0.001</td>
<td>0.053 ±0.004</td>
<td>0.060* ±0.001</td>
<td>0.060* ±0.000</td>
<td>0.060* ±0.000</td>
<td>0.060* ±0.000</td>
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<td>0.060* ±0.000</td>
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<tr>
<td>B</td>
<td>0.057 ±0.001</td>
<td>0.060* ±0.000</td>
<td>0.058 ±0.002</td>
<td>0.060* ±0.000</td>
<td>0.060* ±0.000</td>
<td>0.060* ±0.000</td>
<td>0.059 ±0.000</td>
<td>0.058 ±0.000</td>
<td>0.057 ±0.000</td>
<td>0.060* ±0.000</td>
<td>0.060** ±0.003</td>
<td></td>
</tr>
<tr>
<td>QT interval</td>
<td>A</td>
<td>1.36 ±0.12</td>
<td>1.46* ±0.13</td>
<td>1.53* ±0.13</td>
<td>1.49** ±0.14</td>
<td>1.49** ±0.14</td>
<td>1.52** ±0.13</td>
<td>1.43* ±0.19</td>
<td>1.46* ±0.13</td>
<td>1.17 ±0.15</td>
<td>1.80* ±0.18</td>
<td>1.40* ±0.11</td>
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<tr>
<td>B</td>
<td>1.05 ±0.14</td>
<td>1.05* ±0.18</td>
<td>0.84* ±0.07</td>
<td>1.11 ±0.19</td>
<td>1.08 ±0.19</td>
<td>1.07b ±0.18</td>
<td>1.07b ±0.18</td>
<td>0.95b ±0.16</td>
<td>1.01 ±0.17</td>
<td>1.19* ±0.22</td>
<td>1.40* ±0.21</td>
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<tr>
<td>T wave duration</td>
<td>A</td>
<td>0.056 ±0.010</td>
<td>0.085* ±0.010</td>
<td>0.070 ±0.012</td>
<td>0.070 ±0.010</td>
<td>0.080 ±0.090</td>
<td>0.090* ±0.014</td>
<td>0.090* ±0.100</td>
<td>0.080* ±0.008</td>
<td>0.080* ±0.008</td>
<td>0.080* ±0.008</td>
<td>0.100* ±0.010</td>
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<td>0.075 ±0.007</td>
<td>0.075 ±0.007</td>
<td>0.085 ±0.008</td>
<td>0.100b ±0.005</td>
<td>0.080 ±0.007</td>
<td>0.100b ±0.009</td>
<td>0.210b ±0.060</td>
<td>0.100b ±0.004</td>
<td>0.100b ±0.009</td>
<td></td>
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<tr>
<td>T wave amplitude</td>
<td>A</td>
<td>0.13 ±0.065</td>
<td>0.35 ±0.062</td>
<td>0.31 ±0.058</td>
<td>0.38 ±0.050</td>
<td>0.37 ±0.060</td>
<td>0.36 ±0.061</td>
<td>0.33 ±0.060</td>
<td>0.40* ±0.041</td>
<td>0.48* ±0.011</td>
<td>0.43** ±0.041</td>
<td>0.34 ±0.063</td>
</tr>
<tr>
<td>B</td>
<td>0.18 ±0.080</td>
<td>0.22 ±0.120</td>
<td>0.20 ±0.098</td>
<td>0.17 ±0.120</td>
<td>0.21 ±0.120</td>
<td>0.20 ±0.110</td>
<td>0.21 ±0.120</td>
<td>0.13 ±0.130</td>
<td>0.19 ±0.120</td>
<td>0.34 ±0.100</td>
<td>0.27 ±0.120</td>
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</table>

P wave duration and amplitude

A positive P wave was recorded in all the animals of both groups throughout the study period. The duration of P wave did not change much in both the groups after the administration of the drugs. No significant (P>0.05) differences were recorded in the value of duration of P wave at different time intervals as compared to the respective base values. However, a

P wave was recorded in group A as compared to group B at 10 and 15 min. Thereafter, no significant differences were found between the groups.

In group A, P wave amplitude decreased significantly (P>0.05) at 20 min (P<0.05) and 30 min (P<0.01) and at 60 min (P<0.05). P wave amplitude improved thereafter and did not differ significantly from
75 to 120 min as compared to the base value. In group B, P wave amplitude decreased significantly (P<0.05) at 75 min and this decrease (P<0.01) continued from 90 min to the end of the study. At 10 and 120 min, amplitude in group A was significantly (P<0.01) higher than that of group B.

It has been established that the amplitude of P wave recorded in German Shepherd dogs was related to heart rate; smaller the heart rate, smaller was the amplitude of P wave (Avdosko et al., 2010). Although P wave morphology corresponds to heart rate, however the greatest influence is by autonomic system (Moise, 1998). Dexmedetomidine greatly attenuates sympathetic system, which might be responsible for decreased P wave amplitude in both the groups. Since no significant deviation was observed in group B it may be assumed that midazolam did not have a significant effect on P wave amplitude.

**P-R interval**

In general, an increase in P-R interval was recorded after administration of the drugs in both groups. In animals of group A, P-R interval was significantly (P<0.01) increased at 10 and 20 min after the drug administration and thereafter up to end of the study period.

In the animals of group B, P-R was significantly (P<0.01) increased at 10 min and persisted so thereafter throughout the study period.

Duration of P-R interval reflects conduction of excitation from atria to ventricles, thus its length is closely related to heart rate. Slower heart rate in the animals of the present study might have been responsible for increased P-R interval (Tilley, 1985).

**QRS complex duration and amplitude (R wave)**

In general there was an increase in the duration of QRS complex for variable time period in both groups. In group A, QRS complex duration increased significantly (P<0.05) at 20 min as compared to the base value. Thereafter the increase in the duration of QRS complex was consistent and significant (P<0.05) throughout the period of the observation.

In group B animals, QRS duration increased significantly (P<0.05) at 10 min after the drug administration. It remained significantly (P<0.05) above the baseline values up to 60 min. From 75 min onwards duration of QRS complex decreased towards the baseline and did not vary significantly from the base value up to 120 min.

In the animals of group A, QRS amplitude at 10 min increased non-significantly (P>0.05) from the base value. The amplitude of QRS complex remained increased significantly (P<0.05) at most of the intervals as compared to the base value.

In group B, QRS amplitude was not significantly (P>0.05) different at any point of time from the base value.

QRS complex amplitude at 10 min was significantly (P<0.05) higher in group A as compared to that of group B. At 45 to 75 min, group A amplitude was significantly (P<0.05) higher than that of group B. QRS duration was significantly increased from the base value in both groups A and B. In dogs under ketamine-diazepam anaesthesia, QRS duration increased in Cocker Spaniel dogs whereas in German Shepherd it decreased, implying that QRS duration may be affected by the breed of the dogs (Avdosko et al., 2010). In the present study the dogs belonged to mixed breeds and therefore, variable changes may be expected. QRS (R wave) amplitude was increased in both the groups with a significant increase in group A at 20, 30 and 45 min of study. The results of the present study conform to the findings of Avdosko et al. (2010) who reported increased QRS amplitude in acepromazine premedicated dogs under ketamine-diazepam anaesthesia.

**QT interval**

An increase in QT interval was observed after administration of the drugs in both groups. In group A animals, QT interval increased non-significantly (P>0.05) from the baseline at 10 min. QT interval increased significantly (P<0.01) at 30 min. Thereafter, this increase in QT interval was significant and consistent at all other observation intervals.

The increase in QT interval was more consistent in the animals of groups A and B. QT interval remained increased significantly (P<0.01) from the baseline throughout the period of the study in group B. Duration of QT interval was increased from the base values in both groups significantly up to end of the study period. QT interval varies inversely with heart rate, slower the heart rate longer the QT interval (Tilley, 1985). QT interval is independent of fluctuations in heart rate associated with frequency of ventilation but depends on the mean heart rate. It is also
independent of size and weight of the animal (Oguchi and Hamlin, 1993).

**T wave duration and amplitude**

In general an increase of variable extent and duration was recorded in T wave duration in the animals of both groups after administration of the drugs. In group A, significant ($P<0.01$) increase in the duration of T wave was observed at 10 min following administration of the drug. The duration of T wave remained increased throughout the period of the study and this increase was significant ($P<0.01$) at 105 and 120 min of the study.

In group B, T wave duration increased after administration of the drugs but remained non-significantly ($P>0.05$) higher than the base value throughout the period of the study. In group A, T wave amplitude remained higher than the base value throughout the study period. This increase was significant ($P<0.05$) at 20 and 30 min and highly significant ($P<0.01$) at 90 min.

In group B, a non-significant ($P>0.05$) increase in T amplitude was observed throughout the study period as compared to the base value. The differences between the groups were not significant. The diagnostic value of T wave changes in dogs is very limited in comparison with humans, as T wave morphology is highly variable in small animals (Martin, 2007).

It was concluded that dexmedetomidine and its combination with midazolam produced electrocardiographic changes like sinus arrhythmia, first degree heart block and wandering pace maker were recorded in dogs. Dexmedetomidine alone or in combination with midazolam caused variable changes in P wave duration whereas amplitude was decreased and PR interval increased in both groups. Similarly, QRS complex duration and amplitude increased in both groups. Addition of midazolam did not cause considerable adverse effects on ECG changes induced by dexmedetomidine in dogs.

**References**


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