Effects of propofol and sufentanil on the electrocardiogram of dogs premadeicated with acepromazine

Efeitos do propofol e sufentanil sobre o eletrocardiograma de cães pré-medicados com acepromazina

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Summary: This study was conceived to evaluate the effects of propofol and sufentanil on the electrocardiographic parameters of healthy dogs. Six mature dogs were enrolled in the study. Dogs were premedicated with acepromazine, followed by propofol to induce anesthesia, which was maintained with propofol and sufentanil infused continuously. Every animal underwent three anesthetic procedures at one-week intervals. Each anesthesia was accomplished with a different dose of sufentanil: (G1) 0.025 µg/kg/minute; (G2) 0.05 µg/kg/minute; and (G3) 0.1 µg/kg/minute. Electrocardiograms were recorded at 15 minutes after acepromazine was given (M0), and at 15 (M1), 30 (M2), 60 (M3), 90 (M4), and 120 (M5) minutes after induction of anesthesia. Heart rate, duration and amplitude of P wave, duration of QRS complex, R wave amplitude, PR interval, and QT interval were recorded. ST segment abnormalities and the development of arrhythmias were also searched. Propofol and sufentanil decreased heart rate, and increased PR interval and QT interval in G2 and G3, but failed to do so in G1. The duration of P wave increased significantly in G1 and G3. No significant changes were seen in P wave amplitude, duration of QRS complex, and R wave amplitude. Neither ST segment abnormality nor malignant arrhythmias were observed. The results indicated that the association of propofol and sufentanil seems to affect cardiac electrical conduction and heart rate in a dose-dependent fashion.

Keywords: total intravenous anesthesia; opioids; electrophysiology.

Resumo: Este estudo foi concebido para avaliar os efeitos da associação de propofol e sufentanil sobre os parâmetros eletrocardiográficos de cães saudáveis. Seis cães adultos foram incluídos no estudo. Os animais foram pré-medicados com acepromazina, seguida da indução anestésica com propofol. A manutenção anestésica foi realizada com propofol e sufentanil em infusão contínua. Todos os cães foram submetidos a três protocolos anestésicos diferentes, separados por intervalos semanais, sendo empregada doses diferentes de sufentanil em cada sessão anestésica: (G1) 0,025 µg/kg/minuto; (G2) 0,05 µg/kg/minuto; e (G3) 0,1 µg/kg/minuto. Os traçados eletrocardiográficos foram registrados aos 15 minutos após a aplicação da acepromazina (M0), e aos 15 (M1), 30 (M2), 60 (M3), 90 (M4), e 120 (M5) minutos após a indução anestésica. Foram avaliados a frequência cardíaca, duração e amplitude da onda P, duração do complexo QRS, amplitude da onda R, intervalo PR, e intervalo QT. Também se atentou às eventuais anormalidades no segmento ST e ao desenvolvimento de arritmias. Os dados evidenciaram decréscimo da frequência cardíaca e aumento dos intervalos PR e QT apenas em G2 e G3. A duração da onda P aumentou significativamente em G1 e G3. Contudo, não foram evidenciadas alterações no intervalo da onda P, duração do complexo QRS e amplitude da onda R, assim como no segmento ST. Não se documentou a existência de arritmias malignas. Os resultados apontam que a associação de propofol e sufentanil parece afetar a condução elétrica e frequência cardíaca de maneira dose-dependente.

Palavras-chave: anestesia intravenosa total; opióides; eletrofisiologia.

Introduction

Although inhalational anesthesia seems to be the best option in many conditions in veterinary practice, there are several situations in which a safe protocol of intravenous anesthesia is required for short-term anesthesia in either healthy or diseased dogs (Hellebrekers and Sap, 1997).

Total intravenous anesthesia is obtained through the association of several drugs with distinct actions in the body. When given together, such drugs produce the four basic components of anesthesia: unconsciousness (hypnosis), analgesia, muscular relaxation, and autonomic reflex control (Thurmon et al., 1996).

The pharmacokinetic and pharmacodynamic characteristics of propofol make it the best hypnotic...
agent for induction and maintenance of total intravenous anesthesia (Bembrigde et al., 1993). Propofol is known, however, for not producing a relevant analgesia, which demands its association with analgesic drugs, such as opioids or ketamine (Whitwan et al., 2000).

Mu-agonist opioids like alfentanil, sufentanil, and remifentanil, have been frequently used in association with propofol. Analgesia and hemodynamic stability is achieved during intravenous infusion due to the pharmacokinetic feature of these opioids. Many clinical trials have shown that sufentanil, given as either bolus or continuous infusion, produces an effective analgesia for several surgical procedures (Rosow, 1984). However, it is not completely exempt from side effects, which are related to m receptors located at several organs (Miller et al., 1988).

Regarding the cardiovascular system, Weber et al. (1995) showed that sufentanil reduced the spontaneous depolarization of sinus node in guinea-pig hearts. It also delayed atrioventricular, intraventricular, and His bundle conduction times. In dogs, Blair et al. (1989) showed that sufentanil delayed the action potential on Purkinje cardiac fibers, producing direct effects on cellular membrane. Freye et al. (2000) has also reported that sufentanil reduces heart rate due to its parasympathetic and vagotonic effects.

Therefore, this study was conceived to evaluate the effects of propofol and three increasing doses of sufentanil on the electrocardiographic parameters of healthy dogs premedicated with acepromazine.

Materials and methods

The study was approved by the institutional Committee on the Ethics and Welfare in Animal Experimentation. During the entire experiment, dogs were housed in individual cages and were given free access to water and provided with commercially available dog food twice a day. The study was conducted in accordance with guidelines outlined in the National Institutes of Health - Guide for the Care and Use of Laboratory Animals. The animals were determined to be healthy based on results of both physical and laboratorial examinations prior to the beginning of the experiment.

Six mature mongrel female dogs were enrolled in the study. The dog’s mean body weight was 16.8 ± 2.81 kg (x ± SD). Each animal underwent three anesthetic procedures at one-week intervals. Each anesthesia was performed using a different dose of sufentanil.

After a catheter (Angiocath 20G, Becton Dickinson, Juiz de Fora, Brazil) was inserted through the left cephalic vein, the animals were premedicated with acepromazine (Acepran 0.2%, Univet, São Paulo, Brazil) at 0.05 mg/kg intravenously. Fifteen minutes later, anesthetic induction was accomplished with propofol (Diprivan 1%, AstraZeneca, Cotia, Brazil) at 5 mg/kg given intravenously. The animals were then intubated. Anesthetic maintenance was initiated immediately after induction of anesthesia. For such, two infusion pumps were attached to a three-way stopcock connected to the catheter previously inserted. The first pump (Samtronic 550T2, Samtronic, São Paulo, Brazil) was used for propofol administration (0.2 mg/kg/minute), and the second one (Samtronic 680, Samtronic, São Paulo, Brazil) was used to deliver sufentanil (Sufenta 75 µg/ml, Janssen-Cilag, São José dos Campos, Brazil) in three different doses in accordance with the group to which the animal was allocated: (G1) 0.025 µg/kg/minute, (G2) 0.05 µg/kg/minute, and (G3) 0.1 µg/kg/minute. The infusion of both propofol and sufentanil was discontinued 120 minutes after induction.

To maintain end-tidal carbon dioxide between 35 and 45 mmHg throughout anesthesia, mechanical ventilation was instituted immediately after induction. All dogs were managed with an artificial ventilator (Mechanical ventilator mod. 676, K. Takaoka, São Paulo, Brazil) using volume-limited ventilation (VT = 20 mL/kg). During the study period, respiratory frequency was set at 10 movements per minute, I:E ratio was set at 1:2, and 100% oxygen was provided.

Electrocardiogram was recorded in every animal as described elsewhere (Tilley, 1992). The paper speed was defined as 50 mm/second, and the device was calibrated to 1 cm = 1 mV. Electrocardiographic measurements included: heart rate (HR), duration of P wave (Pms), P wave amplitude (PmV), PR interval (PR), duration of QRS complex (QRS), R wave amplitude (RmV), and QT interval (QT). Changes in ST segment (depression or elevation), and development of malignant arrhythmias were also searched.

Electrocardiographic parameters were measured fifteen minutes after premedication with acepromazine (M0), and at 15 (M1), 30 (M2), 60 (M3), 90 (M4), and 120 (M5) minutes after induction of anesthesia. Each measurement represented the mean of at least three consecutive cardiac cycles in every animal.

A one-way analysis of variance was used to check for differences in electrocardiographic parameters during anesthesia. When differences were determined to exist, data was further analyzed using the post hoc Tukey-Kramer test. We also performed the Student-Newman-Keuls test to check whether different doses of sufentanil played a role in electrocardiographic changes.

Results

Results of electrocardiographic parameters are given in Table 1. Significant differences are reported. Changes in heart rate are shown in Figure 1.
During anesthesia, neither malignant arrhythmias nor abnormal electrocardiographic figures were observed. The most frequent arrhythmia was sinus bradycardia. Such arrhythmia was seen earlier in G2 (from M2 to M5), and G1 (from M3 to M4). Sinus rhythm and sinus arrhythmia were also observed. Also, we did not see either elevation or depression of the ST segment.

Heart rate decreased significantly with anesthesia in G2 ($P=0.0318$) and G3 ($P=0.0256$) (Figure 1). The decrease in heart rate did not attain statistical significance in G1. Individual comparison showed that in G2, M2 was significantly lower than the baseline value, whereas in G3, M2, M3, and M4 were lower than M0. Maximal percentage changes in heart rate were achieved at M4 for G1 (26.25%), at M2 for G2 (26.33%), and at M4 for G3 (25.37%).

Regarding atrial electrical impulse (PmV), baseline values were similar to values during anesthesia in every group. Also, no differences existed in PmV between groups. In all moments, PmV was within the reference range for canines.

The duration of electrical conduction through atrioventricular node (PR interval) was similar among groups. In G2, PR at M5 was significantly greater than baseline measure. In G3, PR at M5 was significantly greater than baseline measure. In G3, PR from M3 to M5 was

### Table 1 - Electrocardiographic parameters in six dogs anesthetized with continuous infusion of propofol (0.2 mg/kg/minute) and increasing doses of sufentanil: G1 (0.025 µg/kg/minute), G2 (0.05 µg/kg/minute), and G3 (0.1 µg/kg/minute). Data expressed as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Group</th>
<th>M0</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>15 minutes</td>
<td>30 minutes</td>
<td>60 minutes</td>
<td>90 minutes</td>
<td>120 minutes</td>
<td>ANOVA</td>
</tr>
<tr>
<td>Pms</td>
<td>G1</td>
<td>39.0 ± 2.0</td>
<td>51.6 ± 7.5</td>
<td>53.3 ± 8.1</td>
<td>55.0 ± 8.3$^*$</td>
<td>55.0 ± 8.3$^*$</td>
<td>60.0 ± 12.6$^*$</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>39.2 ± 8.9</td>
<td>54.4 ± 14.0</td>
<td>52.0 ± 10.9</td>
<td>50.0 ± 10.0</td>
<td>54.4 ± 14.0</td>
<td>50.0 ± 11.5</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>38.2 ± 0.5</td>
<td>46.0 ± 9.5</td>
<td>50.0 ± 11.5$^*$</td>
<td>60.0 ± 2.1$^*$</td>
<td>60.5 ± 10.0$^*$</td>
<td>60.7 ± 15.5$^*$</td>
</tr>
<tr>
<td>PmV</td>
<td>G1</td>
<td>0.18 ± 0.02</td>
<td>0.20 ± 0.03</td>
<td>0.20 ± 0.03</td>
<td>0.17 ± 0.04</td>
<td>0.20 ± 0.03</td>
<td>0.17 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>0.21 ± 0.06</td>
<td>0.21 ± 0.03</td>
<td>0.21 ± 0.05</td>
<td>0.21 ± 0.05</td>
<td>0.21 ± 0.02</td>
<td>0.20 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>0.24 ± 0.08</td>
<td>0.20 ± 0.08</td>
<td>0.20 ± 0.08</td>
<td>0.17 ± 0.05</td>
<td>0.20 ± 0.07</td>
<td>0.21 ± 0.04</td>
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<tr>
<td>PR</td>
<td>G1</td>
<td>90.0 ± 27.5</td>
<td>106.6 ± 27.3</td>
<td>108.3 ± 27.1</td>
<td>123.3 ± 34.4</td>
<td>122.0 ± 29.2</td>
<td>133.3 ± 32.6</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>96.0 ± 21.9</td>
<td>116.4 ± 26.1</td>
<td>130.0 ± 30.0</td>
<td>140.0 ± 34.6</td>
<td>137.6 ± 29.4</td>
<td>155.0 ± 19.1$^*$</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>95.0 ± 16.3</td>
<td>115.0 ± 19.1</td>
<td>125.0 ± 19.1</td>
<td>135.0 ± 19.1$^*$</td>
<td>150.0 ± 20.0$^*$</td>
<td>155.0 ± 23.4$^*$</td>
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<tr>
<td>QRS</td>
<td>G1</td>
<td>41.1 ± 1.6</td>
<td>45.5 ± 7.3</td>
<td>49.1 ± 9.0</td>
<td>54.1 ± 14.3</td>
<td>54.1 ± 14.2</td>
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<tr>
<td></td>
<td>G2</td>
<td>39.4 ± 1.3</td>
<td>41.2 ± 1.7</td>
<td>46.4 ± 8.6</td>
<td>46.6 ± 8.4</td>
<td>42.4 ± 4.3</td>
<td>43.0 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>40.0 ± 1.6</td>
<td>46.7 ± 8.9</td>
<td>50.7 ± 10.6</td>
<td>51.0 ± 10.3</td>
<td>50.7 ± 10.6</td>
<td>50.7 ± 10.6</td>
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<tr>
<td>RmV</td>
<td>G1</td>
<td>1.20 ± 0.22</td>
<td>1.22 ± 0.20</td>
<td>1.17 ± 0.20</td>
<td>1.09 ± 0.26</td>
<td>1.15 ± 0.27</td>
<td>1.14 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>1.19 ± 0.55</td>
<td>1.14 ± 0.46</td>
<td>1.18 ± 0.45</td>
<td>1.15 ± 0.49</td>
<td>1.21 ± 0.46</td>
<td>0.97 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>1.22 ± 0.34</td>
<td>1.40 ± 0.27</td>
<td>1.32 ± 0.41</td>
<td>1.32 ± 0.30</td>
<td>1.36 ± 0.40</td>
<td>1.28 ± 0.35</td>
</tr>
<tr>
<td>QT</td>
<td>G1</td>
<td>232.0 ± 16.0</td>
<td>238.6 ± 26.1</td>
<td>246.6 ± 20.6</td>
<td>256.6 ± 26.5</td>
<td>260.0 ± 25.2</td>
<td>266.0 ± 39.3</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>232.0 ± 10.9</td>
<td>244.0 ± 8.9</td>
<td>260.0 ± 14.1$^*$</td>
<td>262.4 ± 5.3$^*$</td>
<td>269.6 ± 13.4$^*$</td>
<td>265.0 ± 10.0$^*$</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>225.0 ± 19.1</td>
<td>250.0 ± 20.0</td>
<td>245.0 ± 25.1</td>
<td>260.0 ± 23.0</td>
<td>270.0 ± 25.8</td>
<td>265.0 ± 19.1$^*$</td>
</tr>
</tbody>
</table>

Figure 1 - Variation of heart rate in six dogs anesthetized with continuous infusion of propofol (0.2 mg/kg/minute) and increasing doses of sufentanil. M0: Baseline; M1 to M5: 15, 30, 60, 90, and 120 minutes after induction of anesthesia.
greater than baseline value. In all groups, however, maximal percentage changes were achieved at M5 (48.41% for G1; 61.45% for G2; 62.50% for G3).

R wave amplitude (RmV) did not change significantly during anesthesia. Values were within the normal range for dogs. Also, groups were determined to have similar RmV at baseline and throughout anesthesia.

Regarding QT interval, a significant increase was observed in G2 from M2 to M5, whereas in G3, an increase was observed at M4 and M5. When groups were compared, no significant differences existed. In G1, maximal percentage change was achieved at M5 (14.65%), whereas in G2 and G3, it was achieved at M4 (16.20% and 20.00%, respectively).

For all parameters, the Student-Newman-Keuls test did not reveal differences between groups.

Discussion

Dogs tolerated the infusion of propofol and sufentanil with no complications, but the development of sinus bradycardia in some animals. The absence of malignant arrhythmias or shifts in ST segment may indicate that the association of propofol and sufentanil did not result in myocardial oxygenation disturbances (Tilley, 1992).

It is likely that the association of sufentanil and propofol produced bradycardia due to an increase in vagal activity, as was demonstrated by Freye et al. (2000) and Hughes and Nolan (1999). In another study, Flecknell et al. (1990) showed that propofol and alfentanil produced depression of the cardiovascular system in dogs, and suggested that bradycardia was possibly exacerbated by the opioid. After administration of sufentanil in horses, Van Dijk and Nyks (1998) observed bradycardia in all animals and suggested that vagal stimulation had occurred. In cats, Mendes and Selmi (2003) documented a significant reduction in heart rate during total intravenous anesthesia with propofol and sufentanil at 0.01µg/kg/minute. In our study, heart rate did not differ between groups. Therefore, sufentanil failed to cause a dose-dependent parasympathetic effect in this study, contrasting with results of De Hert (1991). When studying the association of sevoflurane and nitrous oxide with two different bolus of sufentanil (0.025 and 0.1 µg/kg), Cardinal et al. (2004) observed an increased risk of developing bradycardia and asystole.

Although the duration of P wave (Pms) was similar among groups, we observed an increase in Pms during anesthesia in G1 and G3. Such findings may be attributable to a delay in atrial electrical conduction due to increased cardiac muscle impedance caused by sufentanil (Weber et al., 1995).

First degree AV block is defined as the prolongation of PR interval greater than 130 milliseconds (Tilley, 1992). In our study, first degree atrioventricular block occurred in a dose-dependent fashion. In G1, first degree AV block was seen only at M5, whereas in G2 and G3, it was recorded from M3 and M4, respectively. The delay in the impulse conduction through the atrioventricular node was likely caused by the dose-dependent vagotonic effect of sufentanil (Bovill, 1993). Studying cardiac electrophysiology, Blair et al. (1989) demonstrated that both fentanyl and sufentanil can delay ventricular depolarization due to a prolonged Purkinje fiber potential, thereby resulting in a longer PR interval. When the effects of sufentanil on guinea-pig hearts were investigated, Weber et al. (1995) observed that such opioid produces effects similar to unspecific calcium antagonists, leading to a significant prolongation in atrioventricular electrical conduction.

Although no differences existed between groups regarding the duration of QRS complex, as well as within each group in relation to baseline measurements, we observed an increase in QRS after the infusion of propofol and sufentanil was initiated. Furthermore, the values of QRS remained slightly higher than the normal reference range for canines (Tilley, 1992). According to Weber et al. (1995), this finding may be related to a prolongation of intraventricular and His bundle conduction times caused by sufentanil.

QT interval is inversely related to heart rate (Oguchi and Hamlin, 1993), which may explain the increasing QT interval during propofol and sufentanil anesthesia. The parasympathetic activity of sufentanil produced a negative chronotropic effect (Blair et al., 1989). The increase in QT interval was also observed by Santos et al. (2001) during desflurane anesthesia in association with fentanyl and droperidol. In the latter study, QT prolongation was ascribed to the parasympathetic activity of fentanyl.

Conclusion

In conclusion, continuous infusion of propofol and sufentanil affects cardiac electrical activity, resulting in a delay in atrioventricular electrical conduction and ventricular depolarization, besides reducing heart rate. Whether such changes may be partially overcome during surgical procedure is yet to be determined.

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Bibliography


