Cardiovascular and pulmonary effects of romifidine and butorphanol combination in horses

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Abstract

The effects of romifidine (60µg/kg) and butorphanol (40µg/kg) combination were studied in eight horses. The parameters were measured before (T0) and 10 (T1), 15 (T2), 30 (T3), 40 (T4) and 65 (T5) minutes after sedation. Heart rate, cardiac output and cardiac index decreased significantly post-treatment. A significant increase was present in pulmonary arterial pressure, pulmonary arterial wedge pressure, central venous pressure and systemic vascular resistance values at post-treatment period. Systolic, mean and diastolic arterial pressures, stroke index and pulmonary vascular resistance did not change significantly. Respiratory rate, mixed venous saturation of oxygen, mixed venous oxygen content and oxygen delivery index decreased significantly post-treatment. Arterial partial pressure of oxygen, arterial saturation of oxygen, mixed venous partial pressure of oxygen, arterial oxygen content, arteriovenous oxygen content difference, oxygen consumption index, oxygen extraction ratio, pH and arterial bicarbonate did not change significantly. The partial pressure of carbon dioxide increased significantly 40 minutes post-treatment. The romifidine and butorphanol combination produced cardiovascular depression similar to those reported with romifidine used alone.

Key-words:
Equine.
Romifidine.
Butorphanol.
Hemodynamics.
Oxygenation.

Introduction

Many diagnostic and surgical procedures might be carried out in horses with less risk to the animal if performed on the conscious, standing subject, than in recumbency. For this to be attempted, predictable, short lived and effective sedation with minimal upset of homeostatic mechanisms is required1.

The alpha-2 agonists have gained wide acceptance as sedative analgesics in the horse. Due to insufficient stability of sedation in current equine practice, these substances are often used in combination with morfine or other opioids to improve sedation and analgesia2. Often these effects are accomplished with a dose reduction of each agent1.

The administration of alpha-2 agonists (xylazine, detomidine and romifidine) to horses produces a variety of behavioral and physiological effects3 and a linear dose/action relationship from light to heavy sedation4.

These agents can produce marked effects on the cardiovascular system including bradycardia, cardiac arrhythmia, second-degree heart block, initial hypertension followed by hypotension, decrease in cardiac output, increase in systemic vascular resistance, and variable changes in arterial blood gases3,6,7. The effects on central nervous system include sedation, muscle relaxation, ataxia, analgesia, vasomotor center depression, and increase in vagal tone and baroreceptor activity3.

The maximal analgesic effect of the alpha-2 agonists is present at 15 minutes and gradually decreases to baseline values after about 60 minutes. Xylazine produces the shortest effect and romifidine the longest8.

Opioids produce their effects by activation of specific receptors in the central and peripheral nervous systems. Systemic
effects of this group of drugs include analgesia, sedation, excitement, increased motor activity, sweating and central dopamine-receptor activation. Muir, Skarda and Shuham demonstrated that the administration of opioids to the adult resting horse results in a drug-dependent increase in heart rate, cardiac output, and arterial blood pressure. Minimal effects on pH and partial pressure of arterial and venous blood gases (PaO₂ and PaCO₂) occur, although respiratory rate is depressed. Butorphanol is a mixed agonist-antagonist opioid. The onset of its action occurs in 2 - 3 minutes, the peak effect between 10 and 30 minutes, and its duration may range from 3 to 4 hours.

Association of romifidine with butorphanol decreases the time of onset of sedation, reduces the response to imposed stimuli and increases the duration of action when compared with romifidine alone. This combination was used to sedate 55 horses for a variety of surgical, therapeutic and diagnostic procedures by Browning and Collins, and they concluded that combination of romifidine and butorphanol is a safe and effective neuroleptanalgesic, and the horses were insensible to aural or tactile stimulation. Taylor, Browning and Harris observed similar effects in clinical use of detomidine associated with butorphanol in 61 horses.

The cardiovascular effects of romifidine and butorphanol used separately at different dosages are already known, and the analgesic effects of the combination are well known experimentally and clinically. However, the cardiovascular effects of the association of these drugs have not been reported. The purpose of the present study was to evaluate the cardiovascular and pulmonary effects of romifidine and butorphanol combination in horses at dosage used in our clinical practice.

**Material and Methods**

Eight healthy male adult horses of different breeds weighing from 353 to 448 kg (mean 415 kg), and between 7 and 23 years old (mean 17 years), were used. Hemogram and physical examination were done 24 hours before sedation. Food, but not water, was withheld for 12 hours before.

The horses were placed in stocks, and the area over the left jugular vein and transverse facial artery were clipped and surgically prepared for aseptic placement of intravascular and intracardiac catheters. Over the left jugular vein, two stab incisions of approximately 0,5 cm, 5 - 8 cm apart, were made through the skin to improve the introduction of a 10 G catheter at each site.

A 120-cm polyethylene tube was introduced through the 10 G catheter placed cranially in the left jugular vein, with its distal opening positioned in the right atrium. A balloon-tipped 7-F 110 cm Swan-Ganz catheter with a thermistor near the tip was introduced through the other 10 G catheter, and the extremity of the catheter was positioned at pulmonary artery. A 22 G catheter was placed through the transverse facial artery. The position of the catheters was confirmed by pressure traces on the monitor. Pressure data were collected by a pressure transducer placed at the level of the shoulder (i.e., level with the left atrium), and the waves recorded in a multiparametric monitor.

After positioning the catheters, a baseline measurement (T₀) was made, and then romifidine at a dose of 60µg/kg and butorphanol at a dose of 40µg/kg were injected, via right jugular vein, in a single bolus. The parameters were measured at 10 (T₁), 15 (T₂), 30 (T₃), 40 (T₄) and 65 (T₅) minutes post-treatment.

**Hemodynamic measurements**

The heart rate (HR) was measured with a multiparametric monitor. Through the transverse facial artery catheter, systolic, mean and diastolic arterial pressures (SAP, MAP and DAP) were measured. The pulmonary arterial pressure (PAP) and pulmonary artery wedge pressure (PAWP) were measured...
through the tip of the Swan-Ganz catheter. The central venous pressure (CVP) was measured through the extremity of the polyethylene tube. The cardiac output (CO) was determined by the thermodilution method with the Swan-Ganz catheter. 40 ml of ice-cold 5% dextrose was injected through the polyethylene tube into the right atrium in 10 seconds, until achieve three values with less than 10% of difference. Parameters calculated and indexed to bodyweight (kg) were: cardiac index (CI), systemic and pulmonary vascular resistance index (SVRI and PVRI) and stroke index (SI).

Oxygenation and ventilation measurements
Respiratory rate (RR) was evaluated by the movement of the thoracic wall. Arterial blood samples were taken from the transverse facial artery catheter using heparin-coated syringes for measurement of arterial partial pressure of oxygen (PaO$_2$), arterial partial pressure of carbon dioxide (PaCO$_2$) and arterial saturation of oxygen (SaO$_2$). Mixed venous samples were taken from the tip of Swan-Ganz catheter for measurement of mixed venous partial pressure of oxygen (PvO$_2$) and mixed venous saturation of oxygen (SvO$_2$). These samples were taken at each measurement time, and kept in a recipient containing iced water until the time of analysis (for about 1 hour and 30 minutes) in a blood gas analysis machine.

Parameters calculated were: arterial oxygen content (CaO$_2$), venous oxygen content (CvO$_2$), arteriovenous oxygen content difference (CavO$_2$), oxygen delivery index (DO$_2$I), oxygen consumption index (VO$_2$I) and oxygen extraction ratio (OER).

Metabolic measurements
Arterial blood samples were used to measure bicarbonate concentration and pH.

Statistical analysis
To test for differences over time, data were analyzed by use of repeated-measures ANOVA, followed by Tukey-Kramer multiple comparisons test. Values of p<0.05 were considered significant.

Results
Hemodynamic measurements results
HR was significantly (P < 0.01) decreased at 10 minutes until 40 minutes after injection of romifidine and butorphanol. At 60 minutes (T5) its values were still reduced, when compared with T0, but not significantly (Table 1). The MAP, SAP and DAP did not demonstrate significant difference between presedation and postsedation (Table 1). The PAP and PAWP were significantly increased 10 minutes after sedation, (respectively, p < 0.001 and p < 0.05) (Table 1). CVP increased significantly at 10, 15 and 40 minutes (respectively, p < 0.001, p < 0.01 and p < 0.01) (Table 1).

CO and CI decreased significantly (P < 0.001) 10 minutes after sedation, and remained reduced in all measurement times (Table 1). SI did not demonstrate significant difference between presedation and postsedation values. The SVRI increased significantly (P < 0.01) at 10 minutes, with a progressive decrease at 15 minutes until 65 minutes (Table 1). Although PVRI did not increase with statistical significance, the values increased at 10 minutes, and then decreased, remaining higher than baseline values until 65 minutes (Table 1).

Oxygenation and ventilation measurements results
The RR decreased with time. At 65 minutes after sedation, the value of RR was significantly (P < 0.001) decreased when compared with baseline (Table 2). PaO$_2$, SaO$_2$ and CaO$_2$ did not decrease significantly (Table 2). PaCO$_2$ increased significantly (P < 0.05) after 40 minutes (P < 0.05). PvO$_2$ did not change significantly (Table 2). SvO$_2$ and CvO$_2$ decreased significantly at 10 minutes (respectively p < 0.01 and p < 0.05) (Table 2). DO$_2$I decreased significantly (P < 0.001) 10 minutes after sedation, and remained reduced until the end of experiment (Table 2).
Table 1 - Mean values and standard deviation of hemodynamic changes in eight horses given combination romifidine (60 µg/kg) and butorphanol (40 µg/kg). São Paulo, 2003

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
</tr>
<tr>
<td>HR</td>
<td>36.1 ±</td>
</tr>
<tr>
<td>beats/minute</td>
<td>10.8</td>
</tr>
<tr>
<td>SAP</td>
<td>144.3 ±</td>
</tr>
<tr>
<td>mm Hg</td>
<td>15.6</td>
</tr>
<tr>
<td>MAP</td>
<td>114.9 ±</td>
</tr>
<tr>
<td>mm Hg</td>
<td>10.8</td>
</tr>
<tr>
<td>DAP</td>
<td>95.1 ±</td>
</tr>
<tr>
<td>mm Hg</td>
<td>13.7</td>
</tr>
<tr>
<td>PAP</td>
<td>19.9 ±</td>
</tr>
<tr>
<td>mm Hg</td>
<td>7.8***</td>
</tr>
<tr>
<td>PAWP</td>
<td>14.6 ±</td>
</tr>
<tr>
<td>mm Hg</td>
<td>8.0</td>
</tr>
<tr>
<td>CVP</td>
<td>4.3 ± 3.7</td>
</tr>
<tr>
<td>mm Hg</td>
<td>24.1 ± 4.9</td>
</tr>
<tr>
<td>CO</td>
<td>4.3 ± 0.8</td>
</tr>
<tr>
<td>L/minute</td>
<td>122.3 ± 115.8</td>
</tr>
<tr>
<td>SVRI</td>
<td>559.4 ± 448.5***</td>
</tr>
<tr>
<td>dynes/sec.</td>
<td>99.6 ± 201.1</td>
</tr>
<tr>
<td>dynes/sec.</td>
<td>26.8</td>
</tr>
</tbody>
</table>

* Significantly different (P < 0.05) from baseline values; ** Significantly different (P < 0.01) from baseline values; *** Significantly different (P < 0.001) from baseline values

2. CavO2, VO2I and OER did not change significantly (Table 2).

Metabolic measurements results

The arterial pH did not change significantly (Table 2). Arterial bicarbonate concentration increased significantly (P < 0.05) at 40 and 65 minutes after sedation (T4) (Table 2).

Discussion

The use of detomidine and butorphanol combination by Clarke and Paton demonstrated that the response to stimuli was greatly reduced and the cardiovascular effects of that association were not exacerbated in horses, when compared with the use of alpha-2 agonists alone. In this study, the cardiovascular effects of the association of romifidine and butorphanol were similar to those related by Freeman et al with romifidine alone in horses.

So, these cardiovascular effects of romifidine and butorphanol combination seem to be due to alpha-2 agonist than the opioid, as shown by Robertson, Muir and...
Table 2 - Mean values and standard deviation of oxygenation, ventilation and metabolic changes in eight horses given combination romifidine (60 µg/kg) and butorphanol (40 µg/kg), São Paulo, 2003

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minutes</th>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>10</td>
<td>15</td>
<td>30</td>
<td>40</td>
<td>65</td>
</tr>
<tr>
<td>RR - respiratory rate per minute</td>
<td>16.1 ± 5.9</td>
<td>12.1 ± 4.7*</td>
<td>12.8 ± 3.7</td>
<td>12.1 ± 3.4*</td>
<td>10.6 ± 3.0**</td>
<td>9.4 ± 3.2***</td>
</tr>
<tr>
<td>PaO2 mm Hg</td>
<td>96.0 ± 8.3</td>
<td>84.9 ± 14.6</td>
<td>82.5 ± 13.8</td>
<td>86.5 ± 14.3</td>
<td>92.5 ± 13.1</td>
<td>94.1 ± 10.8</td>
</tr>
<tr>
<td>PaCO2 mm Hg</td>
<td>34.9 ± 6.5</td>
<td>36.3 ± 5.7</td>
<td>37.3 ± 6.1</td>
<td>40.1 ± 5.9</td>
<td>41.9 ± 3.8*</td>
<td>41.25 ± 4.0</td>
</tr>
<tr>
<td>SaO2 %</td>
<td>97.1 ± 0.8</td>
<td>95.6 ± 2.3</td>
<td>95.5 ± 2.1</td>
<td>96.3 ± 1.7</td>
<td>96.0 ± 1.3</td>
<td>97.0 ± 1.2</td>
</tr>
<tr>
<td>PvO2 mm Hg</td>
<td>34.6 ± 4.3</td>
<td>29.0 ± 4.2</td>
<td>31.6 ± 11.2</td>
<td>31.63 ± 7.4</td>
<td>33.5 ± 13.0</td>
<td>35.0 ± 17.5</td>
</tr>
<tr>
<td>SvO2 %</td>
<td>65.1 ± 8.1</td>
<td>51.3 ± 9.3*</td>
<td>54.5 ± 15.5</td>
<td>57.4 ± 11.7</td>
<td>59.0 ± 14.3</td>
<td>58.5 ± 16.0</td>
</tr>
<tr>
<td>CaO2 ml dl⁻¹</td>
<td>15.5 ± 1.9</td>
<td>15.3 ± 2.0</td>
<td>15.2 ± 2.0</td>
<td>15.4 ± 2.0</td>
<td>15.5 ± 1.9</td>
<td>15.5 ± 1.9</td>
</tr>
<tr>
<td>CVo₂ ml dl⁻¹</td>
<td>10.3 ± 1.8</td>
<td>8.4 ± 1.7*</td>
<td>8.7 ± 2.7</td>
<td>9.1 ± 2.1</td>
<td>9.4 ± 2.6</td>
<td>9.3 ± 2.8</td>
</tr>
<tr>
<td>DO₂ ml min⁻¹.m²</td>
<td>671.8 ± 452.1</td>
<td>499.7 ± 538.9</td>
<td>554.2 ± 526.5</td>
<td>554.2 ± 160.4*</td>
<td>159.4* 128.4**</td>
<td></td>
</tr>
<tr>
<td>VO₂ ml min⁻¹.m²</td>
<td>223.6 ± 204.03</td>
<td>217.70 ± 214.57</td>
<td>215.50 ± 205.39</td>
<td>216.50 ± 84.73</td>
<td>95.42 88.50</td>
<td></td>
</tr>
<tr>
<td>OER %</td>
<td>33.4 ± 8.4</td>
<td>45.0 ± 9.4</td>
<td>43.5 ± 15.2</td>
<td>40.8 ± 12.5</td>
<td>39.6 ± 14.7</td>
<td>40.3 ± 16.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.43 ± 0.03</td>
<td>7.43 ± 0.03</td>
<td>7.43 ± 0.05</td>
<td>7.43 ± 0.04</td>
<td>7.43 ± 0.04</td>
<td>7.44</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>22.6 ± 4.8</td>
<td>25.3 ± 3.7</td>
<td>24.1 ± 4.8</td>
<td>26.0 ± 4.2</td>
<td>27.3 ± 3.7</td>
<td>27.4 ± 4.2</td>
</tr>
</tbody>
</table>

RR = respiratory rate; arterial PaO2 = partial pressure of oxygen; PaCO2 = partial pressure of carbon dioxide; SaO2 = arterial saturation of oxygen; PvO2 = mixed venous partial pressure of oxygen; SvO2 = mixed venous saturation of oxygen; CaO2 = arterial oxygen content; CvO2 = venous oxygen content; CavO2 = arteriovenous oxygen content difference; DO2I = oxygen delivery index; VO2I = oxygen consumption index; OER = oxygen extraction ratio; BIC = bicarbonate.

* Significantly different (P < 0.05) from baseline values; ** Significantly different (P < 0.01) from baseline values; *** Significantly different (P < 0.001) from baseline values.

When the administration of butorphanol to horses led to minimal and not significant cardiovascular effects.

In this series, HR decreased significantly after administration of romifidine and butorphanol. Bradycardia occurred in all 6 horses in 25 seconds after administration of romifidine by Schatzmann, Schmitt and Volgli. Similar results were reported by Polydoro et al, Fantoni et al, Freeman et al and Canola, Cardenas and Canola where significant bradycardia was reported after 10 - 15 minutes of romifidine administration. Bradycardia is thought to be a result of increased vagal tone in response to depression and of baroreceptor stimulation in the carotid sinus in response to initial hypertension caused by the administration of an alpha-2 agonist drug.

A slight increase not significant in...
MAP, SAP and DAP after sedation was expected. After that, values showed progressive decrease. At the end of the study, the values were smaller than the baseline, resembling results recorded by Fantoni and Freeman et al. The transitory increase in arterial pressure values might be due to peripheral post synaptic alpha adrenergic stimulation, resulting in vasoconstriction and hypertension. After this period, the arterial pressure values remain similar to the presedation ones, probably because systemic vascular resistance remains constant, even though with the decrease in the cardiac output.

CVP is determined by intravascular volume status, vascular tone, right heart function and heart rate, and provides information about venous return and cardiac efficiency. However, it must be recognized that the range of values found in normal healthy horses is wide since there is a highly significant correlation between CVP and bodyweight leading to high values of standard deviation. In this study, CVP increased significantly after administration of romifidine and butorphanol until 40 minutes post-treatment. Wagner, Muir and Hinchcliff, found similar results with administration of detomidine and xylazine in horses and Pypendop e Verstegen after administration of romifidine in dogs, and attributed the results to the decrease in the venous capacitance and heart rate. Klein and Sherman suggested that the increase in CVP after alpha-2 agonist administration might be a result of central shift of blood due to systemic vascular resistance increase and a HR decrease.

The alpha-2 agonists’ agents do not seem to influence the pulmonary arterial pressure (PAP). However, in the present study, the PAP increase after administration of romifidine and butorphanol was similar to the results mentioned by Freeman et al and Wagner, Muir Hinchcliff after alpha-2 agonists administration in horses. At the end of the experiment, the PAP had decreased, but was higher than the baseline values. The increase in PAWP values was similar but not so significant. Pypendop e Verstegen attributed this brief increase, after administration of romifidine in dogs, to a response to circulatory stasis related to bradycardia and to an acute increase in left ventricular after load, resulting in blood stasis in the pulmonary capillaries.

In this series, the CO and the CI decreased significantly after sedation and low values remained until the end of the experiment, and the SVI remained constant. Gashuys, De Moor and Parmentier, Wagner, Muir e Hinchcliff, Canola, Cardenas and Canola and Freeman et al found similar results with alpha-2 agonists used alone, and attributed the decrease in CO and CI to decrease in HR. The increase in SVRI, and persistent high values even in the hypotensive phase found in this study, were similar with the use of alpha-2 agonists alone, suggesting a long-lasting peripheral alpha-adrenergic stimulation.

The decrease not significant in PaO2 and SaO2 is similar to previous reports with alpha-2 agonists alone or in combination with opioids. Butorphanol alone was not able to induce significant changes in respiratory rate and blood gases results in Robertson, Muir and sams study. Wagner, Muir and Hinchcliff presume that the decrease in PaO2 is related to an imbalance in perfusion and ventilation, possibly due to a decrease in CO or an increase in PVRI.

The PvO2 provides an assessment of tissue oxygen delivery and blood flow and depends on arterial blood oxygenation, cardiac output and local vasoconstriction. No significant decrease in PvO2 after sedation occurred in this series. The use of romifidine by Freeman et al had similar results, however, the decrease in PvO2 was significant. SvO2 was highly decreased after sedation, and then started to increase, but at the end of the experiment it was still minor than baseline values. Decreases in SvO2 levels frequently indicate an inadequacy of oxygen supply relative to oxygen demand, and may be due to the decrease in SaO2 and CO, and
Efeitos cardiovasculares e pulmonares da associação da romifidina e butorfanol em eqüinos

Resumo

Os efeitos da associação de romifidina (60 µg/kg) com butorfanol (40 µg/kg) i.v. foram avaliados em oito eqüinos. Os parâmetros foram avaliados antes da sedação e 10 (T0), 15 (T2), 30 (T3), 40 (T4) e 65 (T5) minutos após. Os valores da frequência cardíaca, débito cardíaco e índice cardíaco apresentaram redução significativa após a sedação. Um aumento significativo após a sedação foi observado nos valores da pressão da artéria pulmonar, pressão de oclusão de artéria pulmonar, pressão venosa central e índice de resistência vascular sistêmica. Os valores da pressão arterial sistólica, média e diastólica, índice sistólico e resistência vascular pulmonar não apresentaram alterações significativas. Houve redução significativa nos valores da frequência respiratória, saturação de oxigênio no sangue venoso misto, conteúdo de oxigênio no sangue venoso misto e índice de oferta de oxigênio após a sedação. Os valores da pressão parcial de dióxido de carbono, pressão arterial sistólica, média e diastólica, índice sistólico e resistência vascular pulmonar não apresentaram alterações significativas. Um aumento significativo após a sedação foi observado nos valores da pressão da artéria pulmonar, pressão de oclusão de artéria pulmonar, pressão venosa central e índice de resistência vascular sistêmica. Os valores da pressão arterial sistólica, média e diastólica, índice sistólico e resistência vascular pulmonar não apresentaram alterações significativas. Um aumento significativo após a sedação foi observado nos valores da pressão da artéria pulmonar, pressão de oclusão de artéria pulmonar, pressão venosa central e índice de resistência vascular sistêmica. Os valores da pressão arterial sistólica, média e diastólica, índice sistólico e resistência vascular pulmonar não apresentaram alterações significativas. Um aumento significativo após a sedação foi observado nos valores da pressão da artéria pulmonar, pressão de oclusão de artéria pulmonar, pressão venosa central e índice de resistência vascular sistêmica. Os valores da pressão arterial sistólica, média e diastólica, índice sistólico e resistência vascular pulmonar não apresentaram alterações significativas.

Palavras-chave:
Eqüino
Romifidina.
Butorfanol.
Hemodinâmica.
Oxigenação.

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