Evaluation of the effect of hyoscine-N-butyl bromide on the cardiovascular actions of detomidine in the horse

Avaliação do efeito brometo de N-butil hyoscine nas ações cardiovasculares da detomidina em cavalos

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SUMMARY

Twenty one adult horses, males and females, were pretreated with 0.14 mg/kg of hyoscine-N-butylbromide intravenously and injected 5 minutes later with 0.02 mg/kg, iv of detomidine (group A, n = 9) or saline (group B, n = 12). Mean arterial pressure measurements and electrocardiography were performed during 65 minutes. After hyoscine injection the heart rate was increased by 43% and 65% in A and B groups, respectively. Heart rate remained increased after injection of detomidine, returning to baseline values after 15 minutes. No increase in the mean arterial pressure (MAP) was noticed after hyoscine but the MAP was increased by 62% after detomidine, returning to basal measurements until the end of observation time. No additional increase was noted in the group B horses. Hyoscine shortened PR and QT intervals in both groups, but after detomidine, PR and QT intervals enlarged significantly at the end of the experiment. The second degree atrioventricular block occurred in 3 horses after 40 minutes only in group B. It was concluded that hyoscine prevented detomidine induced bradycardia and may be an useful drug combination against the bradycardia induced by this alpha-2 agonist, in horses.

UNITERMS: Scopolamine; Horses; Detomidine.

INTRODUCTION

Detomidine hydrochloride is an alpha-2 agonist drug that produces profound and long acting sedation by reduction of noradrenaline and dopamine release in the central nervous system (CNS)². Both alpha-1 and alpha-2 effects are obtained peripherally, producing vasoconstriction and increased blood pressure³,⁴,¹⁷,¹⁸. Bradycardia is often accompanied by atrioventricular heart block. Approximately 60 minutes after detomidine administration the blood pressure decreases as a result of bradycardia and persistent effects on alpha-2 receptors in the CNS¹². Side effects of detomidine administration include transient reduction in cecal, colonic, and jejunal blood flow⁴. Anticholinergic agents may be used to prevent bradycardia induced by detomidine in horses³. Experiments with medetomidine in dogs¹⁹ showed that pretreatment with atropine was effective against the medetomidine bradycardic effects. Nevertheless, side effects of anticholinergic use are tachycardia, high myocardial oxygen consumption, and intestinal activity reduction³,¹⁶.

Hyoscine-N-butylbromide is a central and peripherally acting anticholinergic widely used as a spasmolytic in the treatment of abdominal pain in horses, that has a shorter pharmacological effect on intestine than atropine in horses¹⁶. Marques et al.¹⁶ showed that hyoscine prevent the bradyarrhythmia produced by romifidine in horses. The purpose of this study was to determine hyoscine effects on the cardiovascular changes induced by detomidine administration in horses.

MATERIAL AND METHOD

Twenty-one adult mixed-breed horses, weighing 371 ± 56 kg, 14 males and 7 females, were divided in two groups (A and B). Weight range in group A was 353 ± 41 kg (range 300 to 430 kg) and in group B was 390 ± 66 kg (range 295 to 515 kg). The horses were held in separate stalls with food and water ad libitum. Stainless steel needle electrodes were placed through the skin at the right forelimb (negative), left forelimb (positive), and placed just behind the left elbow over the area of the cardiac apex for recording
the ECG (VEB ALS 202 - DDR). Both groups received hyoscine-N-butylbromide (Buscopan, Boehringer De Angelis, SP, Brazil) 0.14 mg/kg, iv, through a 20 gauge hypodermic needle. Five minutes later, detomidine hydrochloride (0.02 mg/kg) (Domosedan, Ciba Geigy, SP, Brazil) was injected intravenously into nine experimental animals (group A) or iv saline in equal volume into nine control animals (group B). In twelve horses (6 animals from group A and 6 from group B), a sterile polypropylene catheter - 190 (Medical's Products- SP, Brazil) was inserted aseptically into a facial artery on the ventral surface of the mandible. The catheter was connected to a transducer placed at the cardiac base level for measurement and recording of systolic (SAP) and diastolic (DAP) arterial pressure (Physiograph- DMP-4B Narco Bio-Systems, TA-USA). The mean arterial pressure (MAP) was obtained by calculation DAP + (SAP - DAP)/3. Heart rate (HR), PR and QT intervals were obtained from measurements of the ECG. Lowering of the head and onset of calm behaviour of the horses after drug administration were considered to be clinical signs of sedation. The experiments were conducted in the afternoon.

The horses were maintained in a restraint stock for 30 minutes and then the baseline values for SAP, DAP, MAP, ECG (HR, PR and QT) and behaviour were obtained before injection of hyoscine. Values were recorded 5 minutes later, before injection of detomidine (group A) or saline (group B). Values were recorded again 2 minutes after detomidine or saline injection. Further recordings were made between 10 and 25 minutes at 5 minutes intervals, and then at 10 minutes intervals for a total of 65 minutes.

Statistical analysis

Results are presented as mean ± standard deviation. One-way analysis of variance (ANOVA) was used to evaluate the data, followed by Student-Newman-Keuls test. Difference was considered significant when p ≤ 0.05. To compare the results of the two groups was used the Student paired t-test (p ≤ 0.05).

RESULTS

All results are summarized in the Tab. 1. Baseline heart rate (HR) was 44 ± 8 and 40 ± 5 beats/min. and mean arterial pressure (MAP) was 147 ± 24 (n = 6) and 125 ± 10 (n = 6) mmHg in group A and B, respectively. The hyoscine injection increased the HR to 63 ± 11 beats/min (group A) and 69 ± 15 beats/min (group B) at the 5 minutes and no changes was noted in the MAP (Fig. 1). The heart rate increase was noticed and at the ECG trace was observed shortening of the QT interval from 488 ± 40 to 449 ± 44 milliseconds and 538 ± 29 to 440 ± 45 in the group A and B horses, respectively (Fig. 1). The PR intervals were reduced but no significant changes were observed in both groups, after HBB.

Administration of detomidine resulted in typical behaviour changes in the experimental horses, with sedation and dropped heads. Initially the HR remained elevated, decreasing to baseline values after 15 minutes, and QT significantly lengthened from 45 minutes until the end of the observation time. The PR intervals in the group A were stable and the reduction in the group B was not significant. No arrhythmias were noted until 45 minutes, when atrioventricular heart block was recorded in 3 horses. The AV block occurred regularly at every third to fifth beats. Before administration of detomidine, MAP was 172 ± 24

### Table 1

Cardiovascular changes in horses given hyoscine-N-butyl bromide (HBB) (0.14 mg/kg iv) and following five minutes, detomidine (DET) (0.02 mg/kg iv) or saline (SAL). Jaboticabal, nov. 1995.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Heart rate ± sd (beats/min.)</th>
<th>PR interval ± sd (milliseconds)</th>
<th>QT interval ± sd (milliseconds)</th>
<th>MAP ± sd (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBB DET</td>
<td>HBB SAL</td>
<td>HBB DET</td>
<td>HBB SAL</td>
<td>HBB DET</td>
</tr>
<tr>
<td>0</td>
<td>44 ± 8</td>
<td>40 ± 5</td>
<td>300 ± 37</td>
<td>280 ± 35</td>
</tr>
<tr>
<td>5</td>
<td>63 ± 11*</td>
<td>69 ± 15*</td>
<td>278 ± 21</td>
<td>260 ± 32</td>
</tr>
<tr>
<td>7</td>
<td>58 ± 12*</td>
<td>70 ± 17*</td>
<td>300 ± 25*</td>
<td>258 ± 44</td>
</tr>
<tr>
<td>10</td>
<td>57 ± 10*</td>
<td>71 ± 18*</td>
<td>300 ± 25*</td>
<td>251 ± 30</td>
</tr>
<tr>
<td>15</td>
<td>57 ± 9*</td>
<td>62 ± 8*</td>
<td>313 ± 40</td>
<td>276 ± 37</td>
</tr>
<tr>
<td>20</td>
<td>53 ± 7</td>
<td>57 ± 11*</td>
<td>320 ± 40</td>
<td>291 ± 46</td>
</tr>
<tr>
<td>25</td>
<td>49 ± 6</td>
<td>51 ± 8</td>
<td>329 ± 39</td>
<td>287 ± 45</td>
</tr>
<tr>
<td>35</td>
<td>43 ± 6</td>
<td>47 ± 7</td>
<td>333 ± 40*</td>
<td>284 ± 42</td>
</tr>
<tr>
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<tr>
<td>65</td>
<td>36 ± 8</td>
<td>42 ± 8</td>
<td>338 ± 41</td>
<td>282 ± 43</td>
</tr>
</tbody>
</table>

* - significantly different from time 0 values (p ≤ 0.05 Student-Newman-Keuls test);
** - significantly different from group HBB-SAL (p ≤ 0.05 Student t-test).
HR was increased until 20 minutes after hyoscine. Saline of the experiment (Fig. 1). No arrhythmias were noticed in the control horses.

Comparison between treatments showed that MAP was higher in group A, from 7 to 35 minutes. Baseline QT interval was higher in saline group and decreases after hyoscine injection. In the detomidine treated group QT was increased from 35 until 65 minutes compared to group B. At the group A and B the PR was not different from time zero, and differences between groups at time 7; 10 and 35 to 65 minutes (Fig. 1) were noticed.

**DISCUSSION**

Premedication with an anticholinergic drug is more effective in preventing bradycardia associated with an alpha-2 agonist than treatment of established bradycardia. The detomidine induced bradycardia and atrioventricular block had been correlated with a decrease in the cardiac output. In our study, the hyoscine injection increased the HR and prevented the bradycardia and atrioventricular heart block during the initial period in horses given detomidine, probably through reduction in the vagal activity.

In this study, hyoscine increased heart rate in experimental and control horses. The brief period of tachycardia observed in detomidine treated group may be attributed to the alpha-2 agonist mediated increase in vagal tone, which counteracts the anticholinergic-induced tachycardia.

It has been stated that prolongation and reduction of PR and QT interval may be associated with changes in heart rate. Indeed in our study hyoscine induced tachycardia resulted in QT shortening during 15 minutes in control group. Additionally, in detomidine treated group, cardiac rate reduction was coincident with significant prolongation of QT interval after 45 minutes. The observation of second-degree atrioventricular blocks in three horses was also coincident with QT enlargement but no changes were observed at the same period for the PR intervals. These data suggest that reduction of hyoscine action and the late prevalence of central sympatholytic effect of detomidine may be responsible for the atrioventricular heart block and increased QT interval.

The cardiac effects of detomidine use in horses had been subject of considerable discussion. Atropine injection was recommended to prevent detomidine induced bradycardia. The effect of hyoscine for this purpose has not been previously reported. It is well known that the immediate effect of the intravenous injection of this alpha-2 agonist is vasoconstriction and increased blood pressure by stimulation of post-synaptic adrenoceptors. The mean arterial pressure recorded after hyoscine/detomidine administration was substantially higher than values reported for detomidine alone. It may be that hyoscine induced vagal blockade potentiated detomidine hypertensive action. In a preliminary report, Young et al. observed that atropine sulphate also prevented the heart rate
drop caused by the alpha-2 agonist romifidine and resulted in marked hypertension. Similarly, Marques et al.\textsuperscript{10} described that hyoscine antagonized the romifidine bradycardyamias. Alikbhai et al.\textsuperscript{2} also observed prolonged and intense hypertension when anticholinergic is associated with alpha-2 agonists in dogs. The tachycardia and hypertension observed when hyoscine is used before detomidine may be deleterious by increasing myocardial oxygen demand. Although not investigated in this study, further studies may be indicated to investigate if these effects may be attenuated by intramuscular injection or the use of lower dosages of hyoscine.

The effect of anticholinergic drugs on intestinal motility is of concern in horses. Hyoscine has a shorter duration of action than atropine and reduces peristalsis with no alteration in the electrical pattern\textsuperscript{2,11}. Indeed, the use of atropine in horses had been correlated with prolonged gut stasis and colic\textsuperscript{7}. Although there are no studies comparing the cardiovascular effects of hyoscine and atropine, its use for preventing bradycardia may be preferred to prevent or treat bradycardia in horses because of its shorter action and lower reduction in gastrointestinal motility.

In summary, pretreatment with hyoscine was effective against the arrhythmogenic activity of detomidine, and produced an additional increase in blood pressure. Therefore, its routine use before detomidine must be considered in regard to its hypertensive response.

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RESUMO

Avaliaram-se os efeitos cardiovasculares do N-butilbrometo de hioscina (BBH) associado à detomidina (DET) em eqúinos. Empregaram-se 21 equinos adultos pré-medicados, por via intravenosa (iv), com 0,14 mg/kg de BBH. Decorridos 5 minutos, os animais do grupo A receberam DET na dose de 0,02 mg/kg/fiv e aqueles do grupo B receberam salina. Avaliou-se a pressão arterial média (PAM), atividade cardíaca, por eletrocardiografia (ECG) antes da administração do BBH e, depois, a intervalos de 5 minutos, até os 25 minutos. Após este período, solicitaram-se os dados a cada 10 minutos até os 65 minutos. A administração do BBH aumentou a frequência cardíaca (FC) em 43% e 65%, respectivamente, nos grupos A e B. A FC permaneceu aumentada até 15 minutos da administração da DET. A PAM não aumentou após a administração do BBH, porém foi registrado um aumento de 62% após a aplicação da DET, retomando aos níveis basais ao final do experimento. A aplicação de DET no grupo B não elevou a PAM. A administração do BBH reduziu os intervalos PR e QT em ambos os grupos. Após a aplicação de DET, os intervalos PR e QT aumentaram e foram significativamente maiores ao final do experimento. O bloqueio atrioventricular de 2.° grau (BAV-2.°) ocorreu em 3 animais do grupo B, porém, sempre após 40 minutos da administração da DET. Concluiu-se que o BBH bloqueou a atividade arritmogênica da detomidina e produziu aumento na pressão arterial, a ser considerado quando do emprego dessa associação rotineiramente.

UNITERMOS: Escopolamina; Eqúinos; Detomidina.

REFERENCES


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