CARDIOPULMONARY EFFECTS
OF ACEPROMAZINE-KETAMINE ADMINISTRATION
IN THE SHEEP

ALI BANIADAM, FEREIDOON SABERI AFSHAR,
AND MOHAMMAD REZA BAKRANI BALANI

Department of Clinical Sciences, 1Graduated of Veterinary Medicine,
Faculty of Veterinary Medicine, Shahid Chamran University, 61355-145 Ahvaz, Iran
baniadam@scu.ac.ir

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Abstract

The effects of acepromazine-ketamine on the heart rate, arterial blood pressure, respiratory rate, blood gases, arterial blood pH, and temperature were investigated in six healthy sheep. Ketamine (11 mg/kg i.v.) was given 15 min after administration of acepromazine (0.05 mg/kg i.m.) A catheter was placed in the carotid artery for arterial blood sampling and recording of mean arterial blood pressure. All parameters were evaluated before the administration of acepromazine and at 5, 15, 30, 45, and 60 min following the injection of ketamine. The arterial blood pressure was recorded in 30 s after the injection of ketamine as well. The heart rate decreased significantly at minutes 15, 30, 45, and 60. The mean arterial blood pressure declined significantly at 30 s and 45 min. The mean respiratory rate decreased significantly at 45 and 60 min. PaO₂ decreased significantly at 5, 15, and 45 min, and PaCO₂ increased at 5 min. The pH values decreased significantly at 5, 15, and 30 min. The body temperature decreased significantly at all points in time. The data showed that the combination of acepromazine-ketamine caused an inhibition of the cardiovascular system. This combination is responsible for little distributed ventilation, decreased PaO₂, increased PaCO₂, decreased pH values, and a declined in body temperature in the anaesthesia period in sheep.

Key words: sheep, anaesthesia, acepromazine, ketamine, cardiovascular system, blood gas.

Ketamine has been proved an acceptable anaesthesia for sheep and goats, and can be used on its own, but muscle tone and trembling makes the effect unpleasant, although the analgesia appears to be good (13, 16). The administration of acepromazine in combination with ketamine has distinct advantages. Acepromazine reduces the dosage of ketamine needed for a given period of analgesia, and increases the degree and duration of muscle relaxation, and prevents reflex movements of the limbs. Acepromazine prolongs standing and full recovery times, however (18).

The induction of general anaesthesia is a transition from conscious state to unconsciousness. The body’s systems are usually placed immediately in an unstable state, and undesirable responses from the cardiovascular and respiratory systems may be observed (15). Phenothiazine tranquilisers, such as acepromazine, will markedly decrease systemic blood pressure and heart rate. Dissociative agents, such as ketamine, will substantially increase the heart rate, systemic blood pressure, and a decrease in cardiac contractility (12). In this study, the effect of acepromazine-ketamine on arterial blood pressure, blood gases, pH, heart rate, respiration, and temperature was investigated.

Material and Methods

Six one-year-old Iranian sheep, with an average weight of 22.5 kg, were used. The animals were housed in the teaching hospital of the Faculty of Veterinary Medicine of Shahid Chamran University under conventional conditions. The feed was withheld from all the sheep for 24 h prior to the administration of drugs, but access to water was allowed ad libitum.

The sheep were positioned in a left lateral recumbency on the table, and the lateral surface of the neck was prepared for aseptic surgical intervention. After local anaesthesia, a 5 cm right lateral incision was made to isolate the right lateral carotid artery. The artery
and jugular vein were freed by blunt dissection and isolated. A catheter was advanced in the carotid artery and secured. Acepromazine was administered intramuscularly at the rate of 0.05 mg/kg. Ketamine, 11 mg/kg intravenously, was given 15 min after administration of acepromazine. The animals were not subject to artificial respiration, and no supplemental doses of anaesthetic were given.

Blood samples were drawn through the catheter into a 2 cm³ plastic syringe anaerobically, the inside of which had been coated with heparin. The blood samples were kept on ice and blood gases (PaO₂, PO₂) and pH were measured by a blood gas and acid-base analyser within 60 min. The arterial blood pressure was measured continuously, through the same arterial catheter connected via a fluid-filled line to an aneroid manometer positioned at the level of sternal manubrium. Blood coagulation in catheter was eliminated by frequent flushing with 2/1 000 of a heparinized solution (13). The respiratory rate was recorded by visually counting the respirations. The heart rate was determined by counting beats using a stethoscope. The rectal temperature was recorded by using digital thermometer inserted at least 3 cm into the rectum. Each sheep was allowed to serve as its own control for the experiments. All the parameters were evaluated before the administration of acepromazine and at 5, 15, 30, 45, and 60 min following the administration of ketamine. The arterial blood pressure was recorded at 30 s after the injection of ketamine as well.

The data was analysed, by using the paired student’s t test, SPSS software. Values of P<0.05 were considered significant. All the data was presented as the mean and standard deviation.

### Results

The mean heart rate declined from 84.17 beats/min to 63.83 beats/min, and then increased to 74.5 beats/min at 30- and 60-min intervals, respectively. At the 15-60-min intervals, a significant decline (P<0.05) was observed. At 5-min the mean respiratory rate increased, and then declined gradually at 15- to 60-min post-injection intervals. The respiratory rate values at 45- and 60-min were significantly (P<0.05) lower than before the administration. The mean rectal temperature declined significantly (P<0.05) from baseline at all time points. The mean temperature increased at 60-min but did not reach the baseline (Table 1).

Acepromazine-ketamine produced a marked decline in mean arterial blood pressure at 30 s, which subsequently increased in 5 to 30 min and then remained quite steady. All values of post-injection intervals were lower than the baseline. At 30-s and 45-min, the mean arterial pressure values were significantly (P<0.05) lower than those before injection. Mean PaO₂ decreased at 5 min after ketamine injection and then increased at 15- to 30-min intervals, but did not return to pre-anaesthetic level in 60 min. A significant decrease in PaO₂ (P<0.05) was observed at 5, 15, and 45 min. In contrast, the mean of PaCO₂ increased at 5-min and then decreased at 15- to 60-min post-administration intervals. These values returned to pre-administration level in 60 min, but these changes were significant (P<0.05) only at 5-min. At the 5-min interval, there was a decrease in pH. The decrease was significant (P<0.05) in 5- to 30-min intervals (Table 2). The pH returned to pre-anaesthetic value in 45-min.

#### Table 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>HR (beats/min)</th>
<th>RR (breaths/min)</th>
<th>Temperature (ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84.17 ±18</td>
<td>31.5 ±5.05</td>
<td>39.29 ±0.23</td>
</tr>
<tr>
<td>5</td>
<td>69.33 ±13.68</td>
<td>52 ±25.76</td>
<td>38.28 ±0.23*</td>
</tr>
<tr>
<td>15</td>
<td>66.33 ±14.84*</td>
<td>38.17 ±18.89</td>
<td>38.02 ±0.23*</td>
</tr>
<tr>
<td>30</td>
<td>63.83 ±13.09*</td>
<td>26.33 ±5.01</td>
<td>38.01 ±0.2*</td>
</tr>
<tr>
<td>45</td>
<td>72.67 ±15.98*</td>
<td>23.5 ±3.99*</td>
<td>37.97 ±0.26*</td>
</tr>
<tr>
<td>60</td>
<td>74.5 ±18.52*</td>
<td>21.5 ±1.52*</td>
<td>38.02 ±0.4*</td>
</tr>
</tbody>
</table>

* value significantly different from baseline, P<0.05; ±SD, HR - heart rate; RR - respiratory rate.

#### Table 2

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>MABP (mmHg)</th>
<th>PaO₂ (mmHg)</th>
<th>PaCO₂ (mmHg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>92.5 ±3.78</td>
<td>85.5 ±5.99</td>
<td>40.17 ±1.72</td>
<td>7.47 ±0.03</td>
</tr>
<tr>
<td>5</td>
<td>81.58 ±4.22</td>
<td>61.5 ±11.47*</td>
<td>52.67 ±3.88*</td>
<td>7.38 ±0.031*</td>
</tr>
<tr>
<td>15</td>
<td>85.83 ±6.4</td>
<td>71 ±5.62*</td>
<td>47.5 ±4.8</td>
<td>7.4 ±0.35*</td>
</tr>
<tr>
<td>30</td>
<td>90.17 ±4.71</td>
<td>78.33 ±11.4</td>
<td>42.66 ±3.93</td>
<td>7.44 ±0.029*</td>
</tr>
<tr>
<td>45</td>
<td>85.5 ±2.88*</td>
<td>73.17 ±10.7*</td>
<td>40.66 ±2.42</td>
<td>7.47 ±0.026</td>
</tr>
<tr>
<td>60</td>
<td>88.67 ±4.03</td>
<td>76.33 ±8.64</td>
<td>40.17 ±1.47</td>
<td>7.47 ±0.023</td>
</tr>
</tbody>
</table>

* value significantly different from baseline, P<0.05; ±SD, MABP - mean arterial blood pressure.
Discussion

Although inhalant anaesthetics are generally safer than injectable anaesthetics, their use may be limited by lack of equipment, facilities, or experience of the anaesthetist (5). Veterinarian and scientist must choose the appropriate anaesthesia for surgical procedure in sheep. This study provides information regarding the cardiopulmonary effect of acepromazine-ketamine combination.

In a case study on cats, the heart rates were mildly depressed by acepromazine-ketamine for approximately 15 min and preceded to stabilise, which is similar to our result (2). Other researchers also reported a decrease in the heart rate after acepromazine-ketamine injection in cats (14). Intravenous administration of acepromazine caused insignificant decrease in heart rate and cardiac output in horses (9, 10). The decrease in heart rate was attributed to either a direct adrenergic blocking effect in the heart or to some sort of centrally mediated action, which would have been stronger than reflex tachycardia (9). An increase in heart rates reported to be less among sheep anaesthetised by atropine-acepromazine-ketamine than among sheep anaesthetised by ketamine alone or in a combination with atropine, because acepromazine blocks the pressor response to epinephrine (18). Acepromazine-ketamine significantly increased the heart rate in cats (19) and dogs (3). It was stated, that these changes were due to ketamine sympathomimetic action (19). Verstegen (20) did not find any significant changes after using acepromazine-ketamine in cats. It is suggested that changes in the heart rate in the present study were due to acepromazine. It was thought that sympathomimetic activity of ketamine was masked by acepromazine.

A pattern of apnea has been described after ketamine, atropine-ketamine, and atropine-acepromazine-ketamine injections in sheep. Apnea can be prevented by injecting the drug slowly over a period of 45 to 60 s (18). Mild respiratory inhibition has been reported in ketamine administration and this usually manifests as an increased rate, which does not compensate a decreased tidal volume (4). In this study, the combination of acepromazine-ketamine increased the mean respiratory rate insignificantly, followed by a decrease in respiratory rate. The rate reached a value below a baseline after 30 min. The decline in respiratory rate was reported in cats and rabbits (2, 5).

Phenothiazine tranquilisers produce a haemodynamic effect, predominantly related to their α-adrenergic blocking activity and resultant hypotension (10). Acepromazine given i.v. to horses caused arterial hypotension. The decrease in arterial blood pressure was attributed to acepromazine induced increase in vascular capacity (9, 10). Acepromazine-ketamine also caused a reduction in blood pressure in cats and dogs (1, 2, 14). The effect of acepromazine on mean arterial pressure during romifidine-ketamine-halothane anaesthesia in horses was investigated (11). The acepromazine caused a decline in mean arterial pressure. Ketamine has a short vasodepressor effect within the first few minutes of induction (by relaxing the vascular muscle), followed by a prolonged pressing effect induced by direct central inhibition of baroreceptor activity. The baroreceptors then reflexively increase the sympathetic tone by inhibition of norepinephrine uptake at the adrenergic nerve endings, resulting in peripheral sympathomimetic activity (6). In this study, acepromazine-ketamine caused a marked decrease in the mean arterial blood pressure followed by a decline, which lasted for 60 min. It is suggested that the first effect may be due to a direct relaxation of the vascular smooth muscle within the first minute of induction. The latter is in contrast to the pharmacologic activity of ketamine, which causes a short-lived vasodepressor response that is followed by long-lasting potent depressor response.

The decrease in PaO2 noted after administration of acepromazine-ketamine is attributed to a inhibition of respiratory activity. This change is likely to be due to a decrease in alveolar ventilation, since it has been shown that phenothiazine derived tranquilisers, decrease the respiratory minute volume (17). Direct and indirect relaxation effect of ketamine on bronchial smooth muscle may cause hypventilation and a decrease in blood oxygenation leading to a decline in PaO2. The initial decrease followed by an increase in PaO2 was attributed to the short-lasting depressant effect of ketamine (6, 7). In addition, it is likely that a lateral recumbency caused a decrease in alveolar ventilation of the lungs, resulting in a mismatch of ventilation and perfusion (17). The highest mean PaCO2 was recorded at the 5 min interval. This increase is attributed to a inhibition of respiratory function since it parallels a corresponding decrease in PaO2 (17). Atropine+acepromazine+ketamine in sheep have been shown to cause hypercardia, decrease in pH, and inhibition in PaO2. In the present experiment, the transient decrease in pH, followed by a return to baseline values at 5 to 45 min is in accordance with Thurmon et al. (17) and Muir et al. observations (10). They did not find any significant changes after i.v. administration of acepromazine in horses.

All phenothiazine derivatives including acepromazine cause a fall in body temperature (4). In the present study, rectal temperature declined to 5 to 60 min after the acepromazine-ketamine injection and was consistent with those described for monkeys after using this combination (8).

The data from this study showed that acepromazine-ketamine combination caused inhibition of the cardiovascular system. This combination is responsible for little distributed ventilation, decreased PaO2, increased PaCO2, decreased pH values, and declined body temperature, in the anaesthesia period in sheep. These effects would not be a concern in a healthy animal. However, in an animal with pre-existing respiratory or cardiovascular disease, perhaps some degree of caution may need to be exercised.

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References