The reversal of xylazine hydrochloride by yohimbine and 4-aminopyridine in goats

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ABSTRACT
Yohimbine, 4-aminopyridine, and a combination of the 2 drugs were studied to assess their potential as antagonists to xylazine in goats. Twenty-four small East African goats were divided randomly into 4 groups of 6 goats each in a placebo-controlled study. They were all treated with intramuscular xylazine at 0.44 mg/kg. At the time of maximum sedation, sterile water was administered intravenously to the control group, 0.15% 4-aminopyridine at 0.4 mg/kg to Group 2, 0.1% yohimbine at 0.25 mg/kg to Group 3, and the combination of the 2 drugs at the same dose rates to Group 4. The yohimbine/4-aminopyridine combination was also used to antagonise xylazine at 0.88 mg/kg in 6 goats. The heart rate, respiratory rate and rate of ruminal movements, the pedal and palpebral reflexes as well as the reaction to noxious stimuli, the standing time and the total recovery time were established and evaluated to assess the effects of the treatments. The drugs reversed the xylazine-induced decrease in the heart rate, respiratory rate and rate of ruminal movements, and also rapidly restored the reflexes as well as the reaction to noxious stimulation. In addition, they significantly \( P < 0.05 \) decreased the mean standing time. The mean total recovery time was decreased significantly \( P < 0.05 \) by 4-aminopyridine and the yohimbine/4-aminopyridine combination, but non-significantly \( P > 0.05 \) by yohimbine. No relapse in sedation occurred. Overall, the combination of yohimbine and 4-aminopyridine produced better responses than the individual drugs, and may therefore be used for rapid reversal of xylazine-induced sedation in goats. Yohimbine or 4-aminopyridine may also be useful for this purpose but recovery may be prolonged.

Key words: small East African goats, xylazine antagonists, xylazine hydrochloride, yohimbine, 4-aminopyridine.

MATERIALS AND METHODS
The study involved 24 small East African goats of both sexes weighing 13-25.5 kg and aged 12-36 months. During the study, the goats were housed in indoor pens and were fed with hay, water and mineral licks (Madic®, Twiga Chemicals, Nairobi) ad libitum. Commercial maize bran and maize germ (Unga Feeds, Nairobi) were supplemented regularly.

A preliminary study to determine the doses of 4-aminopyridine and yohimbine to be used in the experiments was performed. This involved administering varying doses of these drugs to groups of 5 non-sedated goats. The dose rates were considered adequate if they produced signs of mild CNS stimulation such as trembling, muscle twitching and vocalisation, without signs of extreme stimulation such as convulsions.

The study was carried out in 2 phases. During the 1st phase the goats were randomly assigned to 4 groups of 6 goats each. The goats were injected with xylazine (Chanazine®, Chanelle Pharmaceutical) intramuscularly at 0.44 mg/kg. At the time of maximum sedation, the goats were injected intravenously with 1ml sterile water (controls, Group 1), 0.15% 4-aminopyridine at 0.4 mg/kg (Group 2), 0.1% yohimbine at 0.25 mg/kg (Group 3), or a combination of both drugs at the same dose rates (Group 4). During the 2nd phase, the combination of 4-aminopyridine (Kyon Lab.) and yohimbine (Kyon Lab.), which produced the fastest recovery in Phase 1, was used to antagonise intramuscular xylazine at 0.88 mg/kg in 6 randomly-selected goats. Control animals were not used because of the risk of xylazine overdose.

After an overnight fasting period, the goats were weighed before being taken to the study area and given a brief period to adjust to their new surroundings and also recover from any excitement. The heart rate, respiratory rate and rate of ruminal movements were then determined and recorded. The heart rate and rate of ruminal movements were determined by auscultation for 1 and 2 minutes respectively, and recorded as beats/minute and contractions/2 minutes respectively. The
Table 1: Effect of sterile water (Group 1), 4-aminopyridine (Group 2), yohimbine (Group 3) and the yohimbine/4-aminopyrine combination (Group 4) on the heart rates of goats sedated with intramuscular xylazine at 0.44mg/kg (mean ± SE).

<table>
<thead>
<tr>
<th>G</th>
<th>BX (mean ± SE)</th>
<th>BA (mean ± SE)</th>
<th>Time after administration of antagonists (minutes)</th>
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<tbody>
<tr>
<td></td>
<td>5</td>
<td>10</td>
<td>15</td>
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<tr>
<td>1</td>
<td>78.3 ± 6.1</td>
<td>54.7 ± 2.9*</td>
<td>53.3 ± 2.5*</td>
</tr>
<tr>
<td>2</td>
<td>67.3 ± 1.4</td>
<td>55.7 ± 1.7*</td>
<td>65.7 ± 2.8*</td>
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<tr>
<td>3</td>
<td>58.3 ± 3.5</td>
<td>43.5 ± 2.7*</td>
<td>51.8 ± 3.3*</td>
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<tr>
<td>4</td>
<td>78.8 ± 6.3</td>
<td>48.8 ± 2.8*</td>
<td>74.5 ± 4.8*</td>
</tr>
</tbody>
</table>

G = group, BX = baseline heart rate, BA = heart rate after xylazine treatment.
*Significantly different (P < 0.05) compared with the pre-xylazine heart rate.
#Significantly different (P < 0.05) compared with the pre-xylazine heart rate.
¶Significantly different (P < 0.05) from the pre-antagonist heart rate.

RESULTS
Doses of 0.44 mg/kg and 0.88 mg/kg of xylazine were adequate to produce sustained recumbency and marked sedation. Onset of signs occurred within 10 minutes of administration.

Reverse of xylazine at 0.44 mg/kg

Xylazine produced a significant decrease (P < 0.05) in heart rate in all groups (Table 1). The administration of the antagonists produced a significant increase (P < 0.05) in heart rate compared with the pre-antagonist value of the same group, but the heart rate was unaltered in the control group. Groups 2 and 4 had significantly (P < 0.05) higher rates compared with the control group, but despite the increase in heart rate in Group 3, there was no significant difference (P > 0.05) compared with the control group.

Xylazine also produced a significant decrease (P < 0.05) in respiratory rate in all groups of goats (Table 2). After the administration of the antagonist drugs, the respiratory rate increased significantly (P < 0.05) compared with the pre-antagonist rate of the same group, but the respiratory rate was unaltered in the control group. In comparison with the control group, the antagonists increased the respiratory rate significantly (P < 0.05) at some of the times assessed. There was no significant

Table 2: Effect of sterile water (Group 1), 4-aminopyridine (Group 2), yohimbine (Group 3) and the yohimbine/4-aminopyrine combination (Group 4) on the respiratory rates of goats sedated with intramuscular xylazine at 0.44mg/kg (mean ± SE).

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<td></td>
<td>5</td>
<td>10</td>
<td>15</td>
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<tr>
<td>1</td>
<td>21.5 ± 1.9</td>
<td>12.0 ± 1.3*</td>
<td>13.0 ± 1.7</td>
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<tr>
<td>2</td>
<td>19.7 ± 1.1</td>
<td>14.0 ± 0.9*</td>
<td>20.0 ± 1.4*</td>
</tr>
<tr>
<td>3</td>
<td>15.2 ± 1.3</td>
<td>9.2 ± 0.6*</td>
<td>15.5 ± 2.5*</td>
</tr>
<tr>
<td>4</td>
<td>21.0 ± 1.6</td>
<td>12.0 ± 1.2*</td>
<td>17.2 ± 1.2*</td>
</tr>
</tbody>
</table>

G = group, BX = baseline respiratory rate, BA = respiratory rate after xylazine treatment.
*Significantly different (P < 0.05) compared with the pre-xylazine respiratory rate.
*Significantly different (P < 0.05) compared with the control group.
*Significantly different (P < 0.05) from the pre-antagonist respiratory rate.
difference (P > 0.05) between Groups 1, 2 and 3.

Xylazine abolished the ruminal contractions at the time of maximum sedation, and this effect persisted for variable time periods in the groups (Table 3). The ruminal movements were recorded first in Group 4 and last in Group 3. They were not recorded in the control group for at least 40 minutes. At some of the times assessed, Groups 2, 3 and 4 had significantly higher (P < 0.05) rate of ruminal movements compared with the pre-antagonist value of the same group and also when compared with the control group.

The antagonists significantly decreased (P < 0.05) the MST, whereas the MTRT was significantly (P < 0.05) decreased in Groups 2 and 4 (Table 4). In Group 3, a slight but not significant reduction in the MTRT was noted. The reduction of both variables was greatest in Group 4, and its MTRT was noted. The reduction of both variables was significant (P < 0.05) from the pre-antagonist rate of ruminal movements. At the time of maximum sedation, there was loss of the noxious stimulation at the flanks, ventral abdomen and around the horns, while the reflexes were absent. Both returned rapidly. The MST and MTRT were 11.6 ± 0.9 and 307.5 ± 2.1 minutes respectively.

Neither relapse to recumbency nor marked sedation were observed in either phase of the study. However, some residual sedation persisted for varying lengths of time. Upon standing, the animals in all groups began to eat hay and maize bran immediately when offered.

Reversal of xylazine at 0.88 mg/kg

The combination of yohimbine and 4-aminopyridine, which produced the greatest reduction in MST and MTRT in the 1st phase of the study, was used to antagonise xylazine at 0.88 mg/kg. Xylazine significantly decreased (P < 0.05) the heart rate, respiratory rate and rate of ruminal movements from pre-xylazine values of 64.8 ± 3.8, 17.8 ± 1.2, and 2.8 ± 0.3 to 49.0 ± 1.6, 14.0 ± 1.9 and 0 respectively, at the time of maximum sedation. The antagonist combination reversed the xylazine-induced decrease in the heart rate and rate of ruminal movements, but produced a slight improvement in the respiratory rate. At the time of maximum sedation, there was loss of the noxious stimulation at the flanks, ventral abdomen and around the horns, while the reflexes were absent. Both returned rapidly. The MST and MTRT were 11.6 ± 0.9 and 307.5 ± 2.1 minutes respectively.

Neither relapse to recumbency nor marked sedation were observed in either phase of the study. However, some residual sedation persisted for varying lengths of time. Upon standing, the animals in all groups began to eat hay and maize bran immediately when offered.

DISCUSSION

Xylazine at 0.2 mg/kg is adequate to induce marked sedation in ruminants. Goats are more sensitive to xylazine than sheep and cattle. The doses of xylazine used in this study were 2 and 4 times the recommended dose in clinical procedures. The effects produced by xylazine at these doses were generally as expected, and are well-documented.

Blockers of the central \(\alpha_2\)-adrenoceptors such as yohimbine, tolazoline, piperoxan, idazoxan and atipamezole have been used to antagonise xylazine in various species. These antagonists act by occupying and interacting with \(\alpha_2\)-adrenergic receptors, thus denying the \(\alpha_2\)-agonists access to these receptors. In the process, they enhance the release of norepinephrine and other excitatory neurotransmitters. They may also be capable of influencing serotonergic, dopaminergic, cholinergic and \(\gamma\)-aminobutyric receptors. Yohimbine is a mixed \(\alpha_2\)-adrenoceptor antagonist, but is more specific for the \(\alpha_2\)-adrenoceptors.

Effects of xylazine are also reversed by the analgetics 4-aminopyridine, doxapram and caffeine, which are physiological antagonists to CNS depressants. The drug 4-aminopyridine acts by facilitating uptake of neuronal calcium ions and enhancing acetylcholine release. It also produces a selective block of potassium ion channels in excitable membranes.

The results obtained in this investigation showed that the administration of 4-aminopyridine, yohimbine or their combination was appropriate to reverse the xylazine-induced bradycardia, bradypnoea and ruminal atony. Similar results were also obtained in cattle and in sheep. At 0.88 mg/kg of xylazine, however, the combination of 4-aminopyridine and yohimbine produced only a slight improvement in the respiratory rates.

The antagonists, alone and in combination, reversed xylazine-induced CNS depression, as evidenced by the rapid return of the reflexes. The 2 selected reflexes are among those used to monitor the level of anaesthesia, and their reappearance is usually interpreted as a sign of acquisition of variable degrees of consciousness. This finding is in agreement with the results of other studies. For instance, in xylazine-treated sheep, yohimbine reduced the time to reappearance of the head-drooping reflex. Yohimbine, 4-aminopyridine and the yohimbine/4-aminopyrine combination significantly increased the MST and MTRT after their administration.
pyridine and their combination were also reported to cause rapid return of front and hind limb withdrawal reflexes in xylazine-treated cattle.

There are conflicting reports on the analgesic effects of xylazine. Some authors have reported persistence of pain even at the maximum depth of sedation. Others have reported adequate analgesia. The presence of analgesia that varied in intensity and duration in various body regions has been reported. It was minimal in the extremities, at the horn base and the flank. In the present study, the reaction to noxious stimuli was consistently present at the limb extremities and scrotal sacs even in the deeply-sedated animals. Analgesia in other body regions was rapidly reversed by the intravenous injection of the antagonists, alone and in combination.

It is very important in goats, as in any other ruminants, to recover to a standing position as soon as possible after sedation or anaesthesia. Hazards of regurgitation, excessive salivation, aspiration and ruminal tympany are present during the recovery period, while the animal is weak and has not regained appropriate control of reflexes and cannot stand up. The antagonists, alone and in combination, significantly reduced the MST, which expresses the time required to gain full control of motor activities. Similar effects have been observed in sheep, cattle and llamas. The reduction was greatest when yohimbine and 4-aminopyridine were combined, followed by 4-aminopyridine alone. The animals were stimulated to stand by hand-clapping, whistling and patting them. This was necessary because sedated animals tend to remain recumbent if not stimulated to stand by hand-clapping.

The antagonists, alone and in combination, also reduced the MTRT, which is the time from the injection of xylazine until overt sedation disappears. The reduction was greatest with the yohimbine/4-aminopyridine combination, followed by 4-aminopyridine alone. Most authors have, however, reported non-significant reductions of the MTRT in xylazine-treated cattle and dogs, and in xylazine/ketamine-anaesthetised horses and goats.

Overall, the combination of yohimbine and 4-aminopyridine produced better responses. The results of this study demonstrated the superiority of the combination of yohimbine and 4-aminopyridine over the individual drugs in antagonising xylazine in goats. The individual drugs may be used for the same purpose but the recovery may be prolonged.

ACKNOWLEDGEMENTS

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REFERENCES