Tolazoline as an Antagonist of Xylazine in Cattle

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ABSTRACT. A study was performed to assess use of tolazoline as an antagonist of xylazine in cattle. Intravenous injection of tolazoline markedly reduced the recovery period from sedation and analgesia when given 15 min after intravenous injection of xylazine in comparison with those that received xylazine + Ringer's solution. Rumen hypomotility and salivation evoked by xylazine were substantially reduced by tolazoline. These results indicate potential usefulness of tolazoline as an antagonist of xylazine in cattle.—KEY WORDS: antagonism, tolazoline, xylazine.

Cattle are characteristically sensitive to xylazine [1, 8, 10]. With a dose sufficient to induce an adequate degree of sedation and analgesia, the drug tends to cause undesirable side effects including bradycardia, bloat and delay in awakening [1, 10, 11], which make it necessary to attend the patient for a considerably long time. A safe antagonist of this potent sedative, therefore, is needed.

In recent years, sedation by xylazine has been reported to be antagonized by yohimbine, an \( \alpha_2 \)-adrenoceptor blocking agent [2, 4–6, 8, 13], but this agent is ineffective in cattle [1, 12]. Tolazoline, another \( \alpha_2 \)-adrenoceptor blocking agent, has been demonstrated to have the antagonistic effect against xylazine in relieving sedation and decreasing rumen motility in ruminants [7, 9, 10, 14].

This study was designed to test whether tolazoline was clinically useful as an antagonist of xylazine.

Six Holstein cows, 4 to 10 years-old, ranging from 396 to 595 kg in weight, were subjected to two identical experiments repeated at an interval of 7 days. Each subject intravenously received xylazine in a single dose of 0.1 mg/kg. Then, they were divided into two group, 1 and 2. Control animals in group 1 were injected with 0.1 ml/kg of Ringer's solution 15 min after the administration of xylazine. Subjects in group 2 received 1 mg/kg of tolazoline as a single injection. The following five parameters were measured in each cow: Recumbency time (time required for the animal to take the position of sternal recumbency), standing time (time required for the animal to stand unassisted), recovery time (time required for overt sedation to disappear), rumen moving time (time required for ruminal movement to reappear), pain returning time (time required for pain sensation to pricking with an injection needle to return), and salivation stopping time (time required for salivation to stop). The time of xylazine injected was taken as 0 min. Heart rates, respiration rates and body temperature were also examined for the initial 180 min.

All the subjects, except one, showed sternal recumbency following the injection, and the mean recumbency time was 4.9 and 4.3 min for group 1 and 2, respectively (Table 1). The one subject remained in a...
standing position throughout the experiment, although it was apparently sedated. Rumen hypomotility and salivation were evident in all the cows after injection with xylazine. The mean standing time and recovery time were 86.2 and 213.3 min in group 1, and 25.4 and 41.8 min in group 2, respectively. Hence, they were significantly shorter (P<0.01) in the latter group than in the former (Table 1). The mean rumen moving time, pain returning time, and salivation stopping time were also significantly shorter (P<0.01) in group 2 than in group 1 (Tables 2 and 3).

Heart rates were significantly higher in group 2 than in group 1 at 120 min (P<0.05) and 180 min (P<0.01). No significant differences were seen in respiration rates and body temperature between the two groups (Table 4).

There have been several reports on antagonists of xylazine in ruminants [1, 3, 7-10, 12]. Kitzman et al. [8] described that in cows injected with yohimbine or 4-aminopyridine after injection with xylazine, standing time was significantly reduced, but recovery time
Table 4. The effect of tolazoline on heart rate, respiration rate and body temperature in xylazine-treated cattle

<table>
<thead>
<tr>
<th>Group a) of cattle</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>46±2</td>
<td>46±4**</td>
<td>46±4**</td>
<td>47±3**</td>
<td>45±3**</td>
<td>45±2**</td>
</tr>
<tr>
<td>2</td>
<td>42±2</td>
<td>44±4**</td>
<td>49±5**</td>
<td>51±10**</td>
<td>57±8</td>
<td>60±6**</td>
</tr>
<tr>
<td>Respiration rate (breaths/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16±13</td>
<td>25±20</td>
<td>19±8</td>
<td>9±3</td>
<td>9±3</td>
<td>10±2</td>
</tr>
<tr>
<td>2</td>
<td>22±17</td>
<td>28±12</td>
<td>11±2</td>
<td>19±27</td>
<td>29±27</td>
<td>31±24</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38.8±0.2</td>
<td>38.9±0.4</td>
<td>38.8±0.4</td>
<td>38.7±0.6</td>
<td>38.5±0.6</td>
<td>38.5±0.6</td>
</tr>
<tr>
<td>2</td>
<td>38.9±0.1</td>
<td>38.9±0.2</td>
<td>38.9±0.3</td>
<td>38.9±0.4</td>
<td>39.0±0.3</td>
<td>39.2±0.3</td>
</tr>
</tbody>
</table>

a) Antagonist (Ringer’s solution for group 1 and tolazoline for group 2) was injected i.v. 15 min. after i.v. injection with xylazine.
b) Mean±S.D.
*, ** Significantly different (*<0.05, **p<0.01) from the value before xylazine injection.
, ′′ Significantly different (′′p<0.05, ′′′p<0.01) from group 1.

showed no changes. Two studies [1, 12], however, demonstrated that yohimbine had no appreciable influence upon sedation induced by xylazine. Doxapram was also effective [3], but no drug has been used widely as an antagonist of xylazine in clinical practice with ruminants.

On the other hand, tolazoline appeared in the literature [7, 9, 10, 14] as a drug showing antagonism to xylazine-induced sedation and gastric hypomotility. The results of the present study clearly indicate that tolazoline has an antagonistic effect against sedation, analgesia and rumen hypomotility induced by xylazine. It also significantly inhibited a decrease in heart rates caused by the drug. No adverse reactions were evident in association with the administration of tolazoline.

From these results, the optimal dose of tolazoline in cattle was estimated to be 1 mg/kg by the intravenous route against a single standard dose of xylazine.

The present investigation indicates the potential clinical applicability of tolazoline as an antagonist of xylazine. It is suggested that tolazoline may be particularly useful for cattle suffering from an overdose effect of xylazine including a delay in recovery from the sedation.

REFERENCES
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要約

牛におけるキシリライン拮抗薬としてのトラゾリンの効果（短報）：高瀬勝寛・日笠喜朗・小笠原成郎（北里大学獣医畜産学部獣医科外科学教室）——牛において、キシリライン0.1mg／kgの静脈内投与でみられた鎮静、鎮痛、第1胃運動の抑制および徐脈はトラゾリン1mg／kgの静脈内投与により明らかに拮抗され、副作用は認められなかった。