Proceedings of the 56th Annual Convention of the American Association of Equine Practitioners

- AAEP -

December 4-8, 2010
Baltimore, Maryland, USA

Next Meeting:
Nov. 18-22, 2011 - San Antonio, Texas, USA

Reprinted in the IVIS website with the permission of the AAEP
Review of Fatalities and Adverse Reactions After Administration of \( \alpha \)-2 Adrenergic Agonist Reversal Agents in the Horse

David B. Scofield, DVM; Dana L. Alexander, BS; Robert P. Franklin, DVM, Diplomate ACVIM; and Joseph J. Bertone, DVM, MS, Diplomate ACVIM

Elective reversal of \( \alpha \)-2 adrenergic receptor agonist sedation with either tolazoline or yohimbine is not without serious risk of idiosyncratic and potentially fatal consequences in the horse; as evidenced by clinical reports of drug reaction and possible death resulting from administration of tolazoline or yohimbine to reverse the effects of \( \alpha \)-2 agonist sedation for veterinary procedures in the horse. Authors’ addresses: Equine Reproduction Laboratory, Colorado State University, Fort Collins, Colorado 80523 (Scofield); Weatherford Equine Medical Center, Weatherford, Texas 76088 (Franklin); and Western College of Veterinary Medicine, Pomona, California 91766 (Alexander and Bertone); e-mail: scofield@colostate.edu. © 2010 AAEP.

1. Introduction

Selective \( \alpha \)-2 adrenergic agonist drugs, such as xylazine HCl,\(^a\) detomidine,\(^b\) and romifidine,\(^c\) represent commonly used sedatives and pre-anesthetics in equine practice. These drugs are sometimes reversed with \( \alpha \)-2 adrenergic antagonists such as yohimbine,\(^d\) atipamezole,\(^e\) and tolazoline.\(^f\) Tolazoline is the only labeled product for the equid; therefore, use of either yohimbine or atipamezole constitutes as extra-label drug use. These reversal agents are deemed as safe pharmacologic products. Anecdotal information, however, suggests that these products can have significant adverse side effects in some cases.

Tolazoline produces strong peripheral vasodilation with sympathetic blocking and histamine-like actions.\(^f\) The drug competitively binds to \( \alpha \)-1 and \( \alpha \)-2 adrenergic receptors, allowing the drug to antagonize the effects of \( \alpha \)-2 agonist sedatives. Therapeutic doses in horses may cause peripheral vasodilation, which clinically leads to a transient increase in heart rate.\(^2\) Toxicity studies report dosages of five times the labeled dose in the horse may cause increased gastric secretions, hyperperistalsis, flatulence, mild colic, or transient diarrhea.\(^3\) These same overdoses could lead to ventricular arrhythmias with prolonged QRS complexes and resultant death.\(^3\) \( \alpha \)-2 Antagonists have been recommended as prokinetics because of their ability to counteract sympathetic outflow related to endotoxin and nociceptive stimuli.\(^4\)

Anecdotal reports of deaths associated with tolazoline reversal have created concern regarding the safety of this drug.\(^5\) Sinus bradycardia, second-degree atrioventricular block, and brief periods of si-
nus arrest occurred after rapid IV administration of tolazoline (1 mg/kg) in five of six xylazine-sedated calves. A case of suspected idiosyncratic tolazoline reaction in a llama has been reported in which the patient exhibited generalized weakness, seizures, dyspnea, severe hypotension, tachycardia, and diarrhea after receiving tolazoline. Both tolazoline and yohimbine, when administered IV, will increase ventricular heart rate for ~30 min after injection.

In dogs, yohimbine blocks central α-2 adrenergic receptors and can cause tachycardia, elevated blood pressure, and stimulation to the central nervous system (CNS). Yohimbine also blocks peripheral α-2 receptors found in the cardiovascular system, genitourinary system, gastrointestinal tract, adipose tissue, and platelets, which can manifest clinically as muscle tremors, tachypnea, and hyperemic mucous membranes.

Administration of α-2 adrenergic antagonists to reverse sedation has resulted in reported idiosyncratic reactions in non-equid species. Animals have died after receiving rapid IV overdoses of yohimbine, atipamezole, or tolazoline. A 1-yr-old female polar bear (Ursus maritimus) immobilized with medetomidine-zolazepam-tiletamine died shortly after reversal from anesthesia with atipamezole administered IV.

The intent of this paper is to document adverse reactions and serious complications encountered when using the α-2 adrenergic antagonists tolazoline and yohimbine to reverse common α-2 adrenergic agonists xylazine, detomidine, and romfidine in the horse.

2. Materials and Methods
Case reports of adverse reactions to administration of either tolazoline or yohimbine for α-2 agonist reversal were solicited from the AAEP List Serve and Equine Clinician’s List Serve in early 2010. Respondents were asked for patient signalment, medical problems, all pharmacologic agents administered, nature of reaction, interventions attempted, outcome of situation, and any postmortem findings if applicable. All data points were not obtained in all cases in the series because of lack of available records in several instances.

Additional information regarding the type of drug used, compounded or labeled product, was incorporated as available. Data were compiled and are presented in Tables 1 and 2.

3. Results
Briefly, 18 total responses were returned to the authors. Of the 18 cases reported via email, mail, and telephone conversations, there were 16 horses comprised of various breeds, 4 mo to 24 yr of age, 1 miniature Donkey, and 1 adult horse of unknown age. Of the 18 responses, 13 animals died despite intervention and resuscitation efforts (Table 2). Five animals recovered with interventions varying from hand walking to the administration of epinephrine via IM injection, dexamethasone IV, and prednisolone sodium succinate IV. Although these resuscitation efforts and pharmacologic interventions were attempted, none clearly altered the outcome for the patient.

Nine of 18 patients were sedated with α-2 adrenergic agonists for dental procedures. Other procedures performed requiring sedation included IV catheter placement, foot trimming, trailer loading, laceration repair, and endoscopy. Three respondents did not report a specific procedure during sedation. Seven respondents reported injections of antagonists at or below the recommended dosages, whereas 11 respondents did not provide dosage information.

4. Discussion
A high number of respondents (13/18) reported ultimate death of the animal in the immediate time frame of administering the reversal agent. All deaths attributed to tolazoline administration were with the product labeled for equine use. Although five yohimbine reactions occurred with compounded products, a Food and Drug Administration-approved canine product (used off-label) was used in three cases. Compounding pharmacies have the ability to alter certain characteristics of the drug such as concentration, delivery vehicles, pH, and storage requirements. In turn, each compounded product may, in fact, have different components that could lead to reactions. Differences in pH, shelf life, solubility, or preservatives from an approved product may alter the actions of the drug in vivo and in turn potentiate adverse side effects. Compounded product drug concentrations were examined post hoc in two cases. Results supported an appropriate concentration of yohimbine in compounded products, although this does not exclude a reaction to the vehicle itself. The cause of negative reaction or death in this case series cannot be definitively attributed to the administration of tolazoline or yohimbine. Circumstantial evidence does support an adverse drug reaction. Other possible causes include intracarotid injection, anaphylaxis, overdosage, confounding medical issues, or unrelated cardiovascular event.

Table 1. Summary of 18 Respondent Case Outcomes in Terms of Drug Use and Outcome

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of Respondents</th>
<th>Outcome</th>
<th>Compounded Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolazoline</td>
<td>7</td>
<td>4 deaths</td>
<td>None</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>11</td>
<td>9 deaths</td>
<td>6 compounded products; 3 labeled canine products; 2 undetermined products</td>
</tr>
<tr>
<td>Signalement</td>
<td>Procedure</td>
<td>Medical Problems</td>
<td>α Agonist</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------</td>
<td>------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Male intact 3-yr-old miniature donkey; 250 kg</td>
<td>IV catheter placement for treatment of broncho-pneumonia</td>
<td>~7-day history of broncho-pneumonia</td>
<td>10 mg IM Detomidine (12 hours prior to reaction) and evening dose of ceftiofur</td>
</tr>
<tr>
<td>6-yr-old Quarter Horse Bay gelding</td>
<td>Routine dental procedure</td>
<td>No known problems</td>
<td>5 mg IV Detomidine</td>
</tr>
<tr>
<td>16-yr-old Warmblood mare</td>
<td>Routine dental procedure</td>
<td>No known problems</td>
<td>5 mg Detomidine IV</td>
</tr>
<tr>
<td>5-yr-old Quarter Horse Bay gelding</td>
<td>Routine dental procedure</td>
<td>No known problems</td>
<td>250 mg Xylazine IV</td>
</tr>
<tr>
<td>6-yr-old Morgan gelding</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>24-yr-old Arabian mare</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>2-yr-old Quarter Horse mare</td>
<td>Tracheotomy and guttural pouch endoscopy</td>
<td>Severe <em>Streptococcus equi sub. equi</em> Infection; azotemia; tracheotomy patent and completed</td>
<td>Xylazine 100 mg and Butorphanol 5 mg IV</td>
</tr>
<tr>
<td>10-yr-old Quarter Horse mare</td>
<td>Unknown</td>
<td>No known medical conditions</td>
<td>Phenylbutazone, Detomidine, and Xylazine</td>
</tr>
<tr>
<td>15-yr-old Quarter Horse Bay gelding</td>
<td>Routine dental procedure</td>
<td>No known medical conditions</td>
<td>Xylazine 600 mg IV and Detomidine 5 mg IV</td>
</tr>
<tr>
<td>Unknown</td>
<td>Routine dental procedure</td>
<td>No known medical conditions</td>
<td>Xylazine and Detomidine mix with unknown dosage</td>
</tr>
<tr>
<td>Signalment</td>
<td>Procedure</td>
<td>Medical Problems</td>
<td>α Agonist</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------</td>
<td>-----------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>4-mo-old Quarter Horse filly</td>
<td>Facial laceration repair</td>
<td>No known medical conditions</td>
<td>2.5 mg Detomidine</td>
</tr>
<tr>
<td>1-yr-old Quarter Horse gelding</td>
<td>Foot trim</td>
<td>No known medical conditions</td>
<td>5 mg Butorphanol IV</td>
</tr>
<tr>
<td>18-yr-old Paint gelding</td>
<td>Foreleg laceration</td>
<td>No known medical conditions</td>
<td>7.5 mg Detomidine</td>
</tr>
<tr>
<td>24-yr-old Appaloosa gelding</td>
<td>Routine dental procedure</td>
<td>No known medical conditions</td>
<td>10 mg Detomidine IV</td>
</tr>
<tr>
<td>1.5-yr-old Thoroughbred filly</td>
<td>Trailer loading</td>
<td>No known medical conditions</td>
<td>100 mg Xylazine IV</td>
</tr>
<tr>
<td>8-yr-old Warmblood gelding</td>
<td>Routine dental procedure</td>
<td>No known medical conditions</td>
<td>5 mg IV Detomidine</td>
</tr>
<tr>
<td>7-yr-old Tennessee Walking cross gelding</td>
<td>Routine dental procedure</td>
<td>No known medical conditions</td>
<td>10 mg Detomidine IV</td>
</tr>
<tr>
<td>9-yr-old Quarter Horse gelding</td>
<td>Routine dental procedure</td>
<td>No known medical conditions</td>
<td>Xylazine and detomidine (unknown dosages)</td>
</tr>
</tbody>
</table>

When data were unavailable, N/A or unknown was substituted in table.
Physiologic responses to the administration of tolazoline and yohimbine may include varying degrees of anxiety, respiratory distress, and cardiovascular compromise. Both drugs, because of their ability to block α-2 adrenergic receptors centrally, peripherally in the distal airway smooth muscle, and in the peripheral vasculature, can cause vasodilation and airway constriction, which may manifest as tachypnea, tachycardia, and anxiety. Although death was not noted in all circumstances, a temporal reaction to a medication may result in owner distress and possibly litigation or further medical issues if damages to the horse, personnel, or property occur during these reactions.

Atipamezole was not included in this case series but has been successfully administered to a pony overdosed with detomidine during a routine castration. Although used in the reported case, atipamezole carries no label claim for the equid and may prove to be cost prohibitive. Furthermore, tolazoline was shown to antagonize detomidine sedation more effectively than atipamezole in the horse. In ponies that were not experiencing any pain, however, α-2 antagonism with tolazoline induced hormonal and metabolic stress responses. Therefore, atipamezole may prove to be a promising agent for use in the horse in the future.

α-2 Agonists are commonly used in equine practice. Overdoses and cardio-depressant events may occur with their administration, necessitating α-2 adrenergic antagonism. Based on this case series, appropriate case selection for α-2 antagonism should be reviewed carefully. Clients should be informed of the possibility of idiosyncratic and potentially fatal reactions from their use. There does not seem to be a predisposing factor to these reactions based on the limited number of cases in this series. A clear mechanism for the adverse reactions from the use of tolazoline or yohimbine has not been identified but likely is caused by cardiopulmonary and CNS events.

In a reported overdose of tolazoline in a llama, resuscitation efforts consisted of IV fluids, oxygen therapy, diazepam IV, and phenylephrine IV. Treatment was successful, and these efforts should be considered for the treatment of an acute reaction to α-2 antagonism. Of note, treatment with either norepinephrine or epinephrine after tolazoline administration will produce a paradoxical decrease in blood pressure, followed by increased blood pressure. In humans, epinephrine is the recommended agent to counteract hypotension after tolazoline administration. Attempts to prevent injury to the animal with soft footing, open spaces, and a lack of noxious stimuli should also be attempted.

The recommended dosages for α-2 antagonists in the horse are as follows: tolazoline, 4 mg/kg, IV, slowly at a rate of 1 ml/s; yohimbine, 0.075 mg/kg, IV (off-label use). To increase the safety of α-2 adrenergic antagonists, the following guidelines should be observed.

1. IM administration: the reversal agent may be given IM, and this is preferred in all but emergency situations because it decreases the risk for CNS excitement or cardiovascular complications.
2. Intravascular administration: administer three separate aliquots equal to one third total IV dose over a 30-min window to prevent sudden cardiopulmonary changes seen with sudden α-2 antagonism.

5. Conclusion

It is understood that no pharmacologic therapy is without risk. However, these cases illustrate that α-2 antagonists have the potential for serious and unpredictable reactions in our equine patients. Veterinarians should be aware of the potential lifethreatening side effects to the use of these drugs and weigh the benefits of their use for non-emergency situations. If one should use tolazoline or yohimbine clinically, they should also be prepared for any reactions to administration and treat them according to clinical presentation. Although there are no firm guidelines for treatment of idiosyncratic reactions to α-2 antagonists, it may be recommended that cardiovascular support with IV fluid therapy and vasoactive drugs such as ephedrine, based on data procured from the human literature or phenylephrine from the veterinary literature, be used in emergent situations For the clinical use of these drugs, we advise following the dosage time frame and routes of administration proposed in the results section above.

Acknowledgments

We thank our respondents from the Equine Clinician’s Network and AAEP Listserv for their candid answers to our queries and for their help during our investigation of these reactions.

References and Footnotes

8. Kollias-Baker CA, Court MH, Williams LL. Influence of yohimbine and tolazoline on the cardiovascular, respiratory,

aTranquiVed, Vedco, St. Joseph, MO 64507.
bDormosedan, Pfizer, Orion, Exton, PA 19341.
cSedivet, Boehringer Ingleheim Vetmedica, St. Joseph, MO 64506.
dYobine, Lloyd, Ben Venue Labs, Bedford, OH 44146.
eAntiseden, Pfizer, Orion, Exton, PA 19341.
fTolazine, Lloyd, Akorn Manufacturing, Decatur, IL 62525.