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Tolazoline: Dose Responses and Side Effects in Non-sedated Holstein Calves

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Abstract

The objective of this study was to investigate the dose response effects of intravenous administration of tolazoline and to characterize the side effects associated with these doses in Holstein calves. Six healthy calves (mean body weight 352.7 ± 87.8 lb; 160.3 ± 39.9 kg) were used in the study. Seven doses (0.23, 0.45, 0.68, 0.91, 1.82, 3.64 and 4.55 mg/lb; 0.5, 1, 1.5, 2, 4, 8 and 10 mg/kg) of tolazoline administered intravenously via jugular vein were studied. Calves were allowed to recover over a period of seven days between each experiment. Heart rate, respiratory rate, mucous membrane color and capillary refill time were recorded before drug administration and at 10 minute intervals for 90 minutes after drug administration. Signs of adverse effects such as anxiety, excitement, CNS depression, salivation, bright red mucous membrane color, sweating, piloerection, trembling, hyperesthesia on the head and neck, muscle weakness, recumbency, dyspnea, abnormal breathing patterns, abdominal pain and diarrhea were recorded. At lower doses (≤0.68 mg/lb; 1.5 mg/kg), administration of tolazoline caused coughing, increased frequency of defecation and mild increase in breathing effort. At higher doses (0.91-4.55 mg/lb; 2-10 mg/kg), adverse effects such as bright red conjunctival mucous membrane, coughing, nasal discharge, salivation, increased breathing effort (labored breathing), CNS depression, signs of abdominal pain, straining, head pressing, restlessness, increased frequency of defecation and diarrhea were observed. All calves recovered.

Keywords: bovine, tolazoline, xylazine, anesthetic, anesthesia

Résumé

L'objectif de cette étude était d'examiner les effets dose suite à l'administration intraveineuse de tolazoline et de documenter les effets secondaires associés à ces doses chez des veaux Holstein. On a utilisé six veaux en santé (poids moyen 352.7 ± 87.8 lb; 160.3 ± 39.9 kg) dans cette étude et examiné l'effet de sept doses (0.23, 0.45, 0.68, 0.91, 1.82, 3.64 et 4.55 mg/lb; 0.5, 1, 1.5, 2, 4, 8 et 10 mg/kg) de tolazoline injectées par voie intraveineuse dans la veine jugulaire. Les veaux bénéficiaient d'une période de sept jours pour recouvrer entre chaque expérience. La fréquence cardiaque, la fréquence respiratoire, la couleur de la muqueuse et le temps de remplissage capillaire étaient notés avant l'administration des doses et ensuite à 10 minutes d'intervalle pendant 90 minutes suivant l'injection. Les effets secondaires étaient notés et incluaient l'anxiété, l'excitation, la dépression du système nerveux central, la salivation, la couleur rouge vif des muqueuses, la sudation, la piloérection, le tremblement, l'hyperesthésie au niveau de la tête et du cou, la faiblesse musculaire, le décubitus, la dyspnée, le rythme anormal de respiration, la douleur abdominale et la diarrhée. Aux plus petites doses (≤0.68 mg/lb; 1.5 mg/kg), l'administration de tolazoline entraina la toux, une plus grande fréquence de défécation et un accroissement léger de l'effort de respiration. Aux plus fortes doses (0.91-4.55 mg/lb; 2-10 mg/kg), les effets secondaires suivants ont été notés: couleur rouge vif de la muqueuse de la conjonctive, toux, écoulement nasal, salivation, accroissement de l'effort de respiration (respiration difficile), dépression du système nerveux central, signes de douleur abdominale, tension, appuyage de la tête, agitation, fréquence plus élevée de défécation et diarrhée. Tous les veaux ont recouvré de leurs symptômes.

Introduction

Xylazine is an α_2 agonist that induces reliable sedation, profound analgesia and good central muscle relaxation. Xylazine is the most popular sedative for use in food animal practice, where it is frequently administered to produce dose-dependent CNS depression, ranging from standing sedation to recumbency.[22,34] Many minor surgical procedures in cattle are performed under xylazine-induced deep sedation, with or without concurrent administration of a local anesthetic.[22,34] To-

lazoline[a] is an α_2 antagonist and is often used to reverse the sedative and immobilizing effects of xylazine.[7,18,32,34] Occasionally, the drug is administered to minimize the adverse effects[12] of xylazine and to treat animals accidentally overdosed with xylazine.[39]

In xylazine-sedated horses, tolazoline returned xylazine-induced gastrointestinal (GI) hypomotility to normal motility.[35] Signs of mild abdominal pain and transient diarrhea were observed in two horses when the drug was administered at three times the recommended dose.[35] Without prior administration of xylazine, tolazoline administered at 1, 3 and 5 times the recommended dose (1.82 mg/lb; 4 mg/kg) induced GI disturbances, such as hypermotility, mild colic and transient diarrhea in horses.[35] Clinical observations indicate that cattle and camelids may be more sensitive to tolazoline than other species. Intravenous (IV) administration of tolazoline at doses recommended for horses (0.91-1.82 mg/lb; 2-4 mg/kg) may cause adverse effects in camelids and cattle,[21] even though similar doses have been given to many other species and no significant adverse effects have been reported.[9,13] Administration of equine doses of tolazoline to domestic ruminants and llamas may result in severe complications such as transient apnea, cardiac arrest, and in llamas, depression and abdominal pain followed by death within 24 hours.[21] There is only one report, however, concerning suspected tolazoline toxicosis in a llama,[20] and in this report a high dose of tolazoline (total 2.45 mg/lb [5.4 mg/kg], half IV and half IM) was administered. Signs of toxicosis included profuse salivation and sweating, anxiety, trembling, hyperesthesia around the head and neck, diarrhea, tachypnea and dyspnea. One of the present authors (Lin personal observation) observed hyperesthesia around the head and neck and dyspnea in one llama, and anxiety and abdominal discomfort in one camel, prior to the present study. Interestingly, the doses of tolazoline used in those two incidents were lower (0.5-0.65 mg/lb; 1.1-1.43 mg/kg IV) than the recommended doses. Current recommendation is to use the lower range of recommended doses, which in ruminants is 0.5-1.0 mg/lb (1.1-2.2 mg/kg).[34] However, no controlled study was conducted to support whether these low recommended doses are safe and will not result in adverse effects. The objectives of this study were to study the dose response of tolazoline over a wide range of doses and to assess the adverse effects associated with administration of these doses in non-sedated Holstein calves.

Materials and Methods

Six healthy, castrated Holstein calves (three to five months of age) with a mean body weight of 352.7 ± 87.8 lb (160.3 ± 39.9 kg) (range 184.6-471.0 lb; 83.9-214.1 kg) were used in this study. The protocol was approved by the Institutional Animal Care and Use Committee of Auburn University. Calves were housed in separate stalls in the Large Animal Teaching Hospital. Water and feed were provided *ad libitum* until the time of experiment. Drug treatment groups studied included: saline (5 ml IV); 0.23 mg/lb (0.5 mg/kg) IV of tolazoline; 0.45 mg/lb (1 mg/kg) IV of tolazoline; 0.68 mg/lb (1.5 mg/kg) IV of tolazoline; 0.91 mg/lb (2 mg/kg) IV of tolazoline; 1.82 mg/lb (4 mg/kg) IV of tolazoline; 3.64 mg/lb (8 mg/kg) IV of tolazoline; and 4.55 mg/lb (10 mg/kg) IV of tolazoline. The order of the treatments began with saline and from lowest dose to higher doses with a one-week interval allowed between each treatment. In order to assure humane treatment and to minimize unnecessary suffering of the animals in case of significant adverse effects, the order of the treatments was not randomly assigned so the study could be terminated at any point. Drugs were administered by IV injection into the jugular vein over 30 seconds. Heart rate (HR), respiratory rate (RR), mucous membrane color and capillary refill time were recorded before drug administration and at 10 minute intervals for 90 minutes after injection. Calves were closely observed during this period. Signs of adverse effects such as anxiety, excitement, CNS depression, salivation, bright red mucous membrane color, sweating, piloerection, trembling, hyperesthesia on the head and neck, muscle weakness, recumbency, dyspnea, abnormal breathing patterns, abdominal pain and diarrhea were recorded. Calves were allowed to recover over a period of seven days between each experiment and were returned to the herd at the end of the study.

One-way ANOVA was used to analyze repeated measures such as heart rate and respiratory rate. A *P*-value less than 0.05 was considered significant.

Results

Significant decreases in HR from 10 to 60 minutes in calves dosed at 0.23 mg/lb (0.5 mg/kg), at 10, 30 and 40 minutes for those dosed at 0.68 mg/lb (1.5 mg/kg), and at 40 and 60 minutes for those dosed at 1.82 mg/lb (4 mg/kg) were observed after receiving tolazoline. A significant increase in HR was observed at 30 and 90 minutes after administration of 3.64 mg/lb (8 mg/kg) of tolazoline. The RR remained unaffected by tolazoline, but a significant increase in RR at 20 minutes and from 60 to 90 minutes was observed after administration of saline. Table 1 shows the mean value ± SD of HR and RR of these calves. Coughing, increased frequency of defecation and mild increase in breathing effort occurred following the administration of 0.23, 0.45 and 0.68 mg/lb (0.5, 1 and 1.5 mg/kg) of tolazoline. Clinical signs of side effects associated with higher doses (0.91, 1.82, 3.64 and 4.55 mg/lb; 2, 4, 8 and 10 mg/kg) included bright red conjunctival mucous membrane, coughing,

Table 1. Mean ± SD of heart rate (HR) and respiratory rate (RR) of calves before (time-0) and at 10-minute intervals following intravenous injection of saline or 0.23, 0.45, 0.68, 0.91, 1.82, 3.64 and 4.55 mg/lb (0.5, 1, 1.5, 2, 4, 8 and 10 mg/kg) of tolazoline.

		0.23 mg/lb	0.45 mg/lb	0.68 mg/lb	0.91 mg/lb	1.82 mg/lb	3.64 mg/lb	4.55 mg/lb
	Saline	0.5 mg/kg	1 mg/kg	1.5 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	10 mg/kg
Heart rate (beats/min)								
0 (Time-0)	87±7.4	94±7.3	64±13.5	77±4.5	76±10.0	77±8.0	72±8.5	83±12.2
minutes								
10	84±10.0	75±11.4*	61±13.9	67±8.8*	74±9.0	75±9.1	71±11.0	90±13.7
20	80±9.0	81±8.7*	64±15.5	73±4.5	77±11.0	73±11.0	77±21.7	90±20.1
30	79±4.5	76±9.0*	62±17.7	68±4.9*	73±11.6	70±7.3	84±22.8*	94±20.1
40	79±5.9	85±7.0*	66±8.8	68±4.9*	73±9.6	67±7.0*	75±17.3	87±16.4
50	79±4.5	83±8.0*	62±9.0	79±8.0	73±10.3	69±8.3	71±16.3	83±21.3
60	82±4.9	82±3.1*	60±13.7	75±8.3	75±8.3	68±8.2*	70±15.0	86±25.1
90	80±10.5	85±8.8	64±11.2	81±8.3	77±5.9	71±8.0	81±21.4*	76±15.5
Respiration rate (breaths/min)								
0	50±10.5	60±17.0	52±14.5	57±10.6	55±18.8	54±20.8	53±11.6	53±15.8
10	56±4.9	60±12.6	54±3.8	51±15.5	52±13.0	57±21.7	52±13.5	54±18.2
20	65±4.5*	65±4.5	57±5.0	53±8.8	55±12.8	51±13.0	52±20.0	48±8.5
30	60±10.7	62±11.8	54±8.5	54±7.6	51±11.8	51±14.1	49±15.4	44±10.0
40	59±7.0	62±17.3	50±9.0	54±7.6	44±8.2	53±16.7	51±14.1	43±5.9
50	60±8.5	53±7.0	54±3.8	59±5.9	48±7.6	53±19.1	44±13.5	47±11.6
60	63±6.3*	64±9.0	53±7.0	55±4.5	60±14	51±16.4	45±11.2	46±9.0
90	67±4.5*	62±13.5	54±7.6	59±5.5	51±11.2	58±17.3	46±17.7	43±10.3

*Significantly changed from time-0 ($P<0.05$)

nasal discharge, salivation, increased breathing effort (labored breathing), CNS depression, signs of abdominal pain, straining, head pressing, restlessness, increased frequency of defecation and diarrhea. Mean frequency of defecation during the 90-minute experiment was 0.5 ± 0.5, 3.3 ± 2.0, 1.8 ± 0.75, 2 ± 0.63, 2 ± 1.41, 2.5 ± 1.97, 4.8 ± 1.3, and 4.3 ± 2.73 for saline, and 0.23, 0.45, 0.68, 0.91, 1.82, 3.64 and 4.55 mg/lb (0.5, 1, 1.5, 2, 4, 8 and 10 mg/kg) of tolazoline, respectively. Regardless of the dose administered, increased frequency of defecation induced by tolazoline was significantly greater than for calves receiving saline. Defecation usually occurred immediately after injection of tolazoline. Some calves coughed during injection of tolazoline, which occurred before the completion of the injection, but coughing did not persist. One calf receiving 1.82 mg/lb (4 mg/kg) and another one receiving 4.55 mg/lb (10 mg/kg) exhibited open-mouth breathing for 30 and 70 minutes, respectively. Two calves receiving 3.64 mg/lb (8 mg/kg) vocalized significantly for 20 to 30 minutes after drug administration. Table 2 summarizes the clinical signs of adverse effects associated with each dose. These clinical signs gradually subsided within 60 to 90 minutes. All calves recovered uneventfully, and no side effects were observed at 24 hours after each experiment.

Discussion

Tolazoline is a 2-benzyl-2-imidazoline, with a chemical structure which resembles several compounds with different activities, including phenylethylamine (the parent compound of catecholamine), histamine (4-imidazolethylamine), clonidine (α_2-agonist), antazoline (H_1-receptor antagonist) and metiamide (H_2-receptor antagonist). With these diverse actions, tolazoline interacts positively and negatively with multiple receptors.[40] The predominant pharmacological effects of tolazoline depend on its selectivity and sensitivity for the receptors and an animal's physical condition.

The result of this study showed that IV administration of tolazoline alone at the doses tested (0.23-4.55 mg/lb; 0.5-10 mg/kg) caused an apparent increase in GI motility and frequent defecation in calves. With the exception of the 0.23 mg/lb (0.5 mg/kg) dose, the effect of tolazoline on GI motility appeared to be dose-dependent, as higher doses were associated with increased

Table 2. Numerical summary of side effects observed in calves following intravenous administration of saline or tolazoline 0.23, 0.45, 0.68, 0.91, 1.82, 3.64 and 4.55 mg/lb (0.5, 1, 1.5, 2, 4, 8 and 10 mg/kg).

		0.23 mg/lb	0.45 mg/lb	0.68 mg/lb	0.91 mg/lb	1.82 mg/lb	3.64 mg/lb	4.55 mg/lb
	Saline	0.5 mg/kg	1 mg/kg	1.5 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	10 mg/kg
Frequency of Defecation	0.5 ± 0.55*	3.3 ± 1.97*	1.8 ± 0.75*	2 ± 0.63*	2 ± 1.41*	2.5 ± 1.97*	4.8 ± 1.33*	4.3 ± 2.73*
No. of calves defecated >1	0/6	5/6	4/6	5/6	4/6	5/6	6/6	6/6
No. of calves attempted to defecate	0/6	4/6	0/6	4/6	5/6	3/6	3/6	3/6
No. of calves with severe abdominal discomfort	0/6	0/6	0/6	0/6	0/6	1/6	4/6	1/6
No. of calves coughed	0/6	0/6	2/6	1/6	2/6	3/6	4/6	5/6
No. of calves with labored breathing	0/6	0/6	0/6	1/6	2/6	2/6	5/6	3/6
No. of calves with nasal discharge	0/6	0/6	0/6	0/6	2/6	0/6	0/6	0/6
No. of calves salivated	0/6	0/6	0/6	0/6	1/6	1/6	0/6	0/6
No. of calves with injected mucous membrane	0/6	0/6	0/6	0/6	0/6	3/6	2/6	5/6
No. of calves were depressed	0/6	0/6	0/6	0/6	0/6	4/6	4/6	1/6

*Significantly changed from time-0 ($P< 0.05$)

frequency of defecation (Table 2). Defecation usually began within minutes following the administration of tolazoline, and watery diarrhea occurred after the second defecation. Explosive diarrhea was not observed at any dose tested in this study. Slight to severe abdominal discomfort and occasional tenesmus occurred in all calves receiving tolazoline treatments, regardless of the dose administered. The degree of discomfort seemed to be dose-dependent, and became more severe and persisted longer at 1.82 mg/lb (4 mg/kg) and higher doses. Signs of abdominal discomfort lessened gradually as the experiment progressed and disappeared toward the end of the experiment.

Defecation has been reported after IV injection of 0.91 and 1.82 mg/lb (2 and 4 mg/kg) of tolazoline to xylazine (0.14 mg/lb; 0.3 mg/kg IM)-sedated calves.[18] However, the frequency of defecation and diarrhea were not reported in that study. In ponies, the potential side effects of GI disturbances were decreased when xylazine was administered prior to tolazoline.[35]

Stimulation of α_2-receptors located in the dorsal vagal nucleus of the medulla oblongata in the CNS[38] and in the GI tract[3] are believed to be responsible for the effects of α_2 agonists on GI motility. In sheep, intracerebroventricular injection of xylazine inhibited reticular contraction.[25] In the gut, stimulation of presynaptic α_2-receptors located at the vagal nerve terminals inhibits acetylcholine release, resulting in reticuloruminal hypomotility, abdominal distension and bloating frequently observed following xylazine administration to ruminants.[3] Tolazoline, with its acetylcholine-like effects, causes hyperperistalsis and diarrhea by stimulating cholinergic receptors.[11] This effect can be prevented by administering atropine.[1] Administration of an α_2-antagonist is thus capable of reversing the GI effect caused by α_2-agonists and returning GI motility back to normal by competing for α_2 receptor binding sites with xylazine.[10] Yohimbine and tolazoline both were reported to reverse xylazine-induced inhibition of reticuloruminal contractions in sheep and cattle, but only tolazoline was able to antagonize the inhibition of secondary ruminal contractions in sheep and alleviate accumulation of gas in the rumen of cattle.[23] In sheep, tolazoline (0.27 mg/lb; 0.6 mg/kg IV) antagonized reticular hypomotility induced by administration of 0.18 mg/lb (0.4 mg/kg) of xylazine.[36] Other studies also indicated that tolazoline reversed xylazine-induced reticuloruminal hypomotility at doses as low as 0.05-0.09 mg/lb (0.1 to 0.2 mg/kg).[10,19,24]

The similarities between the effects of tolazoline and those of histamine include cutaneous vasodilation, conjunctival mucous membrane hyperemia, stimulation of gastric acid and pepsin output, and increased intestinal motility.[1] At least three subtypes of histamine receptors have been identified and are classified as histamine type 1 (H_1), histamine type 2 (H_2) and histamine type 3 (H_3) receptors. Stimulation of H_1 receptors causes respiratory and gastrointestinal smooth muscle contraction and is a causative factor of pruritis and sneezing as a result of sensory nerve stimulation.

Stimulation of H_2 receptors increases gastric acid secretion, myocardial contractility and heart rate. The H_3 receptors are located in the presynaptic postganglionic sympathetic nervous system fibers. When stimulated, these receptors inhibit presynaptic norepinephrine release and histamine synthesis and release.[31] Relaxation of vascular smooth muscles and thus, vasodilation and hypotension, tachycardia, flushing and headache occur when histamine receptors are stimulated. In the present study, we observed clear nasal discharge, prolapsed third eyelid, cutaneous vasodilation and conjunctival injection as evidenced by flushing skin tone and pink to bright red conjunctival mucous membrane. These effects became more apparent and prolonged as the dose of tolazoline increased.

Transient coughing, regardless of the dose of tolazoline administered, occurred halfway through the injection and usually did not reoccur once the injection was completed. Increased breathing effort, which progressed to labored breathing at the highest dose, was observed even though respiratory rate was unaffected. One calf receiving 1.82 mg/lb (4 mg/kg) and another calf receiving 4.55 mg/lb (10 mg/kg) showed open-mouth breathing for 30 and 70 minutes, respectively. Alpha-2 agonists have been shown to attenuate tracheal smooth muscle contractility in response to the electrical field stimulation by inhibition of presynaptic acetylcholine release.[14,15] In these studies, administration of an α_2-antagonist was able to prevent the inhibitory effect of α_2-agonists on tracheal smooth muscle. However, when administered alone these antagonists did not affect the response of tracheal smooth muscles to electrical field stimulation.[14,15] Therefore, it is unlikely that the transient coughing in the calves was α_2-receptor related. Instead, it may be the result of tolazoline-induced histamine release. Perhaps stimulation of H_1 receptors resulting in bronchial smooth muscle contraction in the respiratory tract and stimulation of sensory nerves are responsible for the transient coughing and increased breathing efforts observed in these calves.[27,31] It could not be determined whether the increased breathing efforts and open-mouth breathing pattern are results of poor oxygenation status (low PaO_2) since blood gas values were not monitored in this study. Conflicting results of PaO_2 values—either increased,[6,16,17] unaffected[8] or further decreased[4,19]—after administration of tolazoline, have been reported.

Factors possibly responsible for these variable results include right-to-left shunting through the foramen ovale or through a large patent ductus arteriosus due to a greater reduction in systemic vascular resistance than pulmonary vascular resistance; increased venous admixture as a result of interference with hypoxemic pulmonary vasoconstriction in areas with significant ventilation/perfusion mismatch; and decreased cardiac output, resulting in decreased venous oxygen and/or decreased PaO_2. The first factor would apply only to neonates. Calves in the present study were at least three months old, and were healthy without apparent respiratory disease upon physical examination. Therefore, administration of high doses of tolazoline may have caused a significant decrease in cardiac output which, combined with H_1 receptor-induced respiratory smooth muscle contraction, may have resulted in increased respiratory efforts, panting and open-mouthed breathing observed in these calves.

Dose-dependent CNS depression was observed in several calves receiving ≥1.82 mg/lb (≥4 mg/kg) of tolazoline, but normal attitude returned shortly after the experiment. Abdominal discomfort and inhibition of the release of norepinephrine and histamine associated with stimulation of H_3 receptors[31] may be contributing factors to the CNS depression in these calves.

Tachycardia has been reported as one of the prominent side effects of tolazoline. Yellin *et al* reported positive chronotropic and inotropic effects of tolazoline in guinea pigs which were mediated via cardiac H_2-receptors.[41] However, bradycardia occurred in both normal and hypoxemia-induced pulmonary hypertensive calves following the administration of tolazoline.[37] Tachycardia accompanied by slowing of intraventricular conduction, as reflected in prolonged QRS complex in the electrocardiograph, was observed in horses receiving tolazoline at three to five times the recommended dose.[35] In general, heart rate remained unchanged by tolazoline except with doses of 0.23 and 0.68 mg/lb (0.5 and 1.5 mg/kg), which decreased significantly from baseline. Rapid IV injection has been suggested to cause tachycardia by CNS stimulation. In our study, tolazoline was administered slowly over a 30-second period, which may explain the unaffected heart rate in most of the calves. It was observed that baseline heart rate for calves receiving 0.23 mg/lb (0.5 mg/kg) was higher than those receiving other doses. Although HR in this group after the injection of tolazoline was not different from those receiving other doses, the value was significantly lower than the baseline. Excitement and lack of familiarity with handling in the early phases of the study may explain the higher baseline heart rate. A transient and slight decrease in heart rate occurred at 40 and 60 minutes with 1.82 mg/lb (4 mg/kg), and a transient increase occurred at 30 and 90 minutes with 3.64 mg/lb (8 mg/kg) of tolazoline. The authors believed it was unlikely that these changes were caused by tolazoline due to the delayed occurrence.

Adverse effects of tolazoline reported in humans include abdominal distension, mild to severe GI hemorrhage, renal hemorrhage, hematuria, oliguria, renal failure, hyponatremia, hypotension, hypertension, thrombocytopenia, hyperactivity, seizure and pulmonary hemorrhage.[6] Gastrointestinal ulceration and hemorrhage have been reported to result from tolazoline-in-

duced cholinergic stimulation following treatment of neonatal persistent pulmonary hypertension[2,26,29,30] and peripheral vascular disorder.[40] These adverse effects occurred in patients after being treated for only two days.[6,26] Doses of 0.45, 2.27 and 4.55 mg/lb (1, 5 and 10 mg/kg) of tolazoline administered to one-to-three-day-old lambs caused significant decreases in blood flow to body organs, including spleen, liver and kidney. Blood flow to stomach and intestinal tracts were not affected by tolazoline.[8] As a result, it is unlikely that the adverse effects in GI tracts was due to reduced blood flow to these organs, but more likely due to increased gastric secretion and augmented histamine-induced contractions in the intestines.[1,5,40] This is further supported by the observation that tolazoline-induced gastric acid secretion is abolished by administration of H_2-antagonists, metiamide and burimamide.[41] We did not observe severe adverse effects after repeat administration of tolazoline in these calves, although dose-dependent abdominal discomfort and tenesmus were observed. All calves had normal behavior and appetite, and normal feces were produced 24 hours after each experiment and at one week after the completion of the study. Similarly, no clinically significant side effects were observed in calves receiving 3.0 mg/lb (6.6 mg/kg) of tolazoline for reversal of xylazine-induced sedation.[33]

The result of the present study indicated that administration of 0.23, 0.45 and 0.68 mg/lb (0.5, 1 and 1.5 mg/kg) of tolazoline were not associated with GI and respiratory effects. The frequency and degree of severity of GI motility and discomfort as well as respiratory effort increased at doses greater than 0.68 mg/lb (1.5 mg/kg). In cattle, the recommended dose of tolazoline is 0.5 to 1.0 mg/lb (1.1 to 2.2 mg/kg IV), but the high recommended dose (1.0 mg/lb; 2.2 mg/kg) is advised for treatment of accidental overdosing of xylazine.[34] Riebold commented on the variation in dosage and toxicity between llamas and other species, and suggested that 50% of the calculated dose (0.45-0.91 mg/lb; 1-2 mg/kg IV) should be administered initially and this dose repeated if necessary.[21] Powell *et al*[18] studied the efficacy of tolazoline in reversing 0.14 mg/lb (0.3 mg/kg) of xylazine-induced sedation in calves. The mean arousal times for calves receiving 0.45, 0.91 and 1.82 mg/lb (1, 2 and 4 mg/kg) of tolazoline were 4.7±3.8, 0.9±0.5 and 0.7±0.3 minutes, respectively, as compared to 27.8±11.5 minutes in those that did not receive tolazoline.[18] It is apparent that tolazoline administered at a dose as low as 0.45 mg/lb (1 mg/kg) was effective in reversing xylazine-induced CNS depression. In addition, the side effects of tolazoline are somewhat offset by the presence of xylazine when the drug is administered to antagonize xylazine's pharmacological effects. Therefore, IV administration of 0.23, 0.45 and 0.68 mg/lb (0.5, 1 and 1.5 mg/kg) of tolazoline are not associated with adverse effects and can be used safely and effectively to reverse xylazine-induced sedation in cattle and llamas.

Conclusions

In cattle, the recommended dose of tolazoline is 0.50-1.0 mg/lb (1.1 to 2.2 mg/kg IV), but the upper recommended dose (1.0 mg/lb; 2.2 mg/kg) is only advised for treatment of accidental overdosing of xylazine. Clinical observations in ruminants and camelids have demonstrated the variation in dosage and toxicity between these two species and other species, and that 50% of the calculated dose (0.45-0.91 mg/lb; 1-2 mg/kg IV) should be administered initially; this dose can be repeated if necessary. The result of the present study showed that administration of 0.23, 0.45 and 0.68 mg/lb (0.5, 1 and 1.5 mg/kg) of tolazoline was not associated with GI or respiratory effects, and can be used safely and effectively to reverse xylazine-induced sedation in cattle. The frequency and the degree of severity of GI motility and discomfort and respiratory effort increased at doses greater than 0.68 mg/lb (1.5 mg/kg).

Endnotes

[a]Tolazine®, Lloyd Laboratory, Shenandoah, IA

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