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Effectiveness of tolazoline in reversing xylazine-induced sedation in calves

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Objective—To test effectiveness of IV administration of tolazoline hydrochloride in reversing xylazine hydrochloride-induced sedation in calves.

Design—Prospective study.

Animals—12 female and 12 male Friesian-cross calves from 5 to 7 months old.

Procedure—Calves were assigned to 1 of 4 treatment groups. Calves were given xylazine (0.3 mg/kg [0.14 mg/lb] of body weight, IM). Twenty minutes later, calves were treated with saline (0.9% NaCl) solution (1 ml/50 kg [1 ml/110 lb], IV) or tolazoline (1, 2, or 4 mg/kg [0.45, 0.9, or 1.8 mg/lb], IV). Behavioral and physiologic measurements included elapsed time from xylazine administration to recumbency, arousal and standing times after reversal drug administration, heart rate, and respiratory rate.

Results—Mean (± SD) recumbency time for all calves was 5.4 ± 1.8 minutes. Compared with administration of saline solution, all 3 doses of tolazoline significantly decreased arousal and standing times. Mean arousal time for calves receiving saline solution was 27.8 ± 11.5 minutes. Administration of tolazoline at 1, 2, and 4 mg/kg resulted in mean arousal times of 4.7 ± 3.8, 0.9 ± 0.5, and 0.7 ± 0.3 minutes, respectively. Mean standing time for calves receiving saline solution was 38.8 ± 2.8 minutes. Administration of tolazoline at 1, 2, and 4 mg/kg resulted in mean standing times of 14.0 ± 11.0, 3.0 ± 1.2, and 2.4 ± 1.1 minutes, respectively.

Clinical Implications—For routine use, tolazoline doses of 1 to 2 mg/kg should suffice. In cattle, IV administration of tolazoline reverses pharmacologic effects of xylazine, thereby hastening recovery from xylazine-induced sedation. (*J Am Vet Med Assoc* 1998;212:90–92)

Xylazine hydrochloride[a] is an α_2-adrenergic receptor agonist that produces sedation, analgesia, and muscle relaxation when administered parenterally to animals.[1] Ruminants, particularly domestic cattle, are among the animals most sensitive to the action of xylazine.[2] The dose administered to produce deep sedation and analgesia in cattle is generally a tenth of the dose recommended in horses, dogs, and cats. The dose range commonly recommended for IM administration is 0.05 mg/kg (0.02 mg/lb) of body weight for mild sedation, 0.2 mg/kg (0.09 mg/lb) for moderate sedation, and 0.3 mg/kg (0.14 mg/lb) for heavy sedation. Doses of 0.2 to 0.3 mg/kg regularly result in recumbency. Prolonged recumbency, hypothermia, ruminal atony, labored respiration, and excessive salivation are often observed.[3] Ruminal atony may result in bloating with possible regurgitation and aspiration pneumonia.[4] These complications can be minimized by judicious use of tolazoline hydrochloride as a reversal agent, allowing cattle to be aroused and safely stand within minutes of administration.[5]

Tolazoline[b] is an antiadrenergic drug that is a mild, nonselective, α_1- and α_2-adrenergic receptor antagonist that will reverse CNS α_2-mediated sedation and sympathetic depression of an α_2- adrenergic receptor agonist, such as xylazine.[2,6] Tolazoline is used in human medicine as a peripheral vasodilator to treat persistent pulmonary hypertension in newborns.[7] The purpose of the study reported here was to test effectiveness of 3 doses of tolazoline in reversing xylazine-induced sedation in calves.

Materials and Methods

Animals and study design—Twelve female and 12 castrated male Friesian-cross calves from 5 to 7 months old and weighing 86 to 164 kg (190 to 362 lb; mean ± SD, 117 ± 19 kg [258 ± 42 lb]) were used in the trial. Calves were quiet, accustomed to being handled, and kept in confinement together in a grass pasture. Calves ate grass and drank water ad libitum for 1 week before testing. They were blocked by weight and sex and randomly assigned to 4 treatment groups. Therefore, each group had 3 females and 3 males, with similar mean body weights among treatment groups. Calves were identified with ear tags and body paint. All were observed by a veterinarian to be healthy and clinically normal and were weighed and confined in a paddock just prior to the study.

Each calf was given xylazine (0.3 mg/kg, IM). Twenty minutes later, calves were treated with saline (0.9% NaCl) solution or 1 of 3 dosages of tolazoline administered IV via the jugular vein. Calves were grouped in 1 of the following 4 treatment groups: group-1 (control group) calves received saline solution at 1 ml/50 kg (1 ml/110 lb), group-2 calves received tolazoline at 1 mg/kg (0.45 mg/lb), group-3 calves received tolazoline at 2 mg/kg (0.9 mg/lb), and group-4 calves received tolazoline at 4 mg/kg (1.8 mg/lb). The observer was blinded relative to reversal drug administered (saline solution vs tolazoline) and dose used.

Measurements—Each calf was evaluated, using various behavioral and physiologic measurements to determine reversal effects of tolazoline on xylazine-induced sedation. Recumbency time was the time from xylazine administration to lying down. Arousal time was the time from reversal drug administration to awakening (defined as first intentional head movement). Standing time was the time from reversal

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drug administration to standing up. For each calf, an arousal score was determined 10, 20, or 30 minutes after administration of reversal drug by use of the following ranking scores: 1 = walking with normal gait; 2 = walking directionally with slightly ataxic gait; 3 = walking directionally with ataxic gait; 4 = standing but unable to walk in any coordinated pattern; 5 = recumbent but aroused; and 6 = recumbent and not aroused. **Heart rate (HR)** and **respiratory rate (RR)** were measured by auscultation of the thorax at four 5-minute periods. Times used for HR and RR determinations included the following: 15 to 10 minutes before xylazine administration, 10 to 15 minutes after xylazine administration, 30 to 35 minutes after xylazine administration (10 to 15 minutes after reversal drug administration), and 50 to 55 minutes after xylazine administration (30 to 35 minutes after reversal drug administration). Each calf was observed for 60 minutes after xylazine administration, and any abnormal clinical sign not related to pharmacologic effects of xylazine was recorded.

Statistical analysis—Data were analyzed by use of a statistical program[c] to test pharmacologic effects of tolazoline. An ANOVA was used to compare arousal status and physiologic measurements at each time period among treatment groups. As post hoc analyses, Dunnett's procedure was used to compare results from each tolazoline treatment group with the control group at each period, and Fisher's LSD method was used to compare results from all treatment groups. Results are expressed as mean ± SD. Values of $P < 0.01$ (Dunnett's procedure) and $P < 0.05$ (Fisher's LSD method) were considered significant.

Table 1—Mean (± SD) effects of IV administration of tolazoline in reversing xylazine-induced sedation in calves

Variables	Control (0.9% NaCl) 1 ml/50 kg (1 ml/110 lb) n = 6	Tolazoline 1 mg/kg (0.45 mg/lb) n = 6	Tolazoline 2 mg/kg (0.9 mg/lb) n = 6	Tolazoline 4 mg/kg (1.8 mg/lb) n = 6
AT (min)	27.8 ± 11.5[a]	4.7 ± 3.8[b,*]	0.9 ± 0.5[b,*]	0.7 ± 0.3[b,*]
ST (min)	38.8 ± 2.8[a]	14.0 ± 11.0[b,*]	3.0 ± 1.2[c,*]	2.4 ± 1.1[c,*]
AS10	5.8 ± 0.4[a]	4.7 ± 1.0[b,*]	3.2 ± 0.4[c,*]	2.3 ± 0.5[d,*]
AS20	5.7 ± 0.5[a]	3.5 ± 1.4[b,*]	2.0 ± 0.6[c,*]	1.0 ± 0.0[c,*]
AS30	5.3 ± 0.8[a]	2.2 ± 1.0[b,*]	1.2 ± 0.4[c,*]	1.0 ± 0.0[c,*]
HR1 (beats/min)	82.7 ± 4.1[a]	79.7 ± 7.2[a]	77.3 ± 7.4[a]	84.0 ± 11.9[a]
HR2 (beats/min)	66.0 ± 7.6[a]	62.3 ± 6.6[a,b]	57.3 ± 5.3[b]	56.7 ± 5.9[b]
HR3 (beats/min)	66.3 ± 4.1[a]	66.0 ± 6.1[a]	64.0 ± 4.7[a]	78.0 ± 4.0[b,*]
HR4 (beats/min)	63.2 ± 5.2[a]	65.7 ± 4.8[a]	66.3 ± 3.9[a]	84.3 ± 11.6[b,*]
RR1 (breaths/min)	53.3 ± 6.0[a]	42.3 ± 13.4[a]	49.3 ± 5.5[a]	43.7 ± 12.0[a]
RR2 (breaths/min)	32.0 ± 25.7[a]	22.3 ± 7.7[a]	35.0 ± 18.8[a]	33.2 ± 15.5[a]
RR3 (breaths/min)	25.3 ± 16.8[a]	25.7 ± 11.7[a]	29.2 ± 15.9[a]	40.8 ± 13.4[b]
RR4 (breaths/min)	29.0 ± 24.7[a]	28.7 ± 12.4[a]	36.0 ± 13.9[a]	35.8 ± 6.9[a]

*Significantly ($P < 0.01$) different from control values, using Dunnett's procedure.

AT = arousal time; ST = standing time; AS10, AS20, and AS30 = arousal score at 10, 20, and 30 minutes after administration of reversal drug; HR1, HR2, HR3, HR4 and RR1, RR2, RR3, RR4 = heart rate (HR) and respiratory rate (RR) at 15 to 10 minutes before (HR1, RR1), 10 to 15 minutes after (HR2, RR2), 30 to 35 minutes after (HR3, RR3), and 50 to 55 minutes after (HR4, RR4) xylazine administration.

Values in a row without common superscripts differ significantly ($P < 0.05$), using Fisher's LSD method.

Results

Recumbency time after IM administration of xylazine ranged from 2.1 to 9.2 minutes, with a mean value of 5.4 ± 1.8 minutes. Mean HR and RR 10 minutes before and 10 minutes after xylazine administration were 80.9 ± 8.0 beats/min, 60.6 ± 7.1 breaths/min, 47.2 ± 10.3 beats/min, and 30.6 ± 17.6 breaths/min, respectively. Two group-1 calves panted after receiving xylazine and continued shallow, rapid breathing throughout the observation period. In group-1 calves, xylazine administration resulted in a profound and lasting sedative effect (Table 1). All group-1 calves, except one, remained recumbent for 60 minutes after xylazine administration. One group-1 calf stood briefly after receiving saline solution administered IV but fell back into a recumbent position and remained recumbent until the end of the trial.

Compared with group-1 calves, group-2 calves had significantly shorter arousal and standing times and significantly lower arousal scores 10, 20, and 30 minutes after tolazoline administration (Table 1). There was, however, no significant difference in group-1 and group-2 calves in terms of HR and RR during any of the 5-minute periods measured. By the end of the observation period, 2 group-2 calves were clinically normal, 1 was only slightly ataxic, and 3 were ataxic with directional gait.

Compared with group-1 calves, group-3 calves also had significantly shorter arousal and standing times and significantly improved (lower, more awake) arousal scores without a significant effect on HR and RR (Table 1). Group-3 calves were usually awake within 1 minute after administration of tolazoline and were standing in about 3 minutes. At the end of the observation period, 5 of 6 group-3 calves had a normal gait. Most group-3 calves urinated shortly after standing and a few defecated, but none had any outward signs of distress or discomfort. One calf was observed to have a reddening of its muzzle and nose.

Compared with group-1 calves, group-4 calves had significantly shorter arousal and standing times and significantly lower arousal scores, with effects varying in significance for HR and RR (Table 1). Group-4 calves were awakened more quickly, stood sooner, and regained normal gait sooner than group-3 calves, but these differences were not significant except at 10 minutes after receiving reversal drug. For group-4 calves, tolazoline administration resulted in HR returning to values before sedation; however, RR were only increased slightly above values for group-1 calves. Only 1 group-4 calf had a RR greater than the value before sedation, whereas 3 of 6 group-4 calves ended the trial with HR slightly above values before sedation. Outward signs of excitement were not observed in group-4 calves, and although most urinated and a few defecated after tolazoline administration, they did not have any clinical signs of distress. All group-4 calves were assessed as having normal gait 20 minutes after tolazoline administration (40 minutes after xylazine administration).

Calves receiving tolazoline in this study were not observed to have any signs of distress or excitement. Calves in all 4 treatment groups were capable of free movement and were grazing at the end of the observation period.

Discussion

Results of this study confirm that IM administration of xylazine at 0.3 mg/kg induces effective sedation and immobilization in calves. Xylazine-induced sedation lasted for more than 50 minutes in calves that received saline solution (group-1 calves), which is a

longer period than required for many surgical or diagnostic procedures in cattle. Although not observed in this study, this dose of xylazine may be relatively unsafe, resulting primarily from adverse gastrointestinal effects in recumbent cattle.[8]

Results of this study also indicate that IV administration of tolazoline at all 3 doses is effective in reversing xylazine-induced sedation and immobilization in calves. Greatest improvement in reversal of sedation in terms of decreased arousal time was observed in group-3 and group-4 calves, which received tolazoline at 2 mg/kg and 4 mg/kg, respectively. However, a dose of 4 mg/kg may be necessary to reverse xylazine-induced bradycardia and respiratory depression. These higher doses of tolazoline resulted in quick reversal of the sedative effects of xylazine, allowing calves to regain reflexes and stand within a few minutes after tolazoline administration. Results of other studies[5,d] indicate that tolazoline administration in xylazine-treated cattle improves gastrointestinal tract mobility and smooth muscle tone (eg, urinary bladder tone). Doses of tolazoline as low as 0.1 to 0.2 mg/kg (0.045 to 0.09 mg/lb) will reverse reticuloruminal amotility induced by xylazine administration in cattle.[3,4,9]

[a]Xylazine injection, Parnell Labs Aust Pty Ltd, Alexandria, Australia.
[b]Tolazine injection, LLOYD Inc, Shenandoah, Iowa.
[c]SYSTAT Inc, Evanston, Ill.
[d]Young DB, Shawley RV, Barron SJ. Tolazoline reversal of xylazine-ketamine anaesthesia in calves (abstr). *Vet Surg* 1988;18:171.

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