Antagonistic Effects of Alpha-adrenoceptor Blocking Agents on Reticuloruminal Hypomotility Induced by Xylazine in Cattle

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ABSTRACT

The intravenous injection of a standard dose (0.05 mg/kg) of xylazine inhibited reticuloruminal motility in cattle. Pretreatment with adrenoceptor antagonists showing α_2-blocking activity, tolazoline (0.5 mg/kg) and yohimbine (0.2 mg/kg), antagonized the xylazine-induced reticuloruminal amotility. Tolazoline was more effective than yohimbine, since an antagonistic effect was not seen at 0.5 mg/kg yohimbine, and yohimbine at 0.2 mg/kg was less effective than tolazoline at 0.5 mg/kg. An adrenoceptor antagonist showing α_1-blocking activity, prazosin, did not prevent the inhibition of reticuloruminal motility by xylazine. The xylazine-induced reticuloruminal amotility was also not prevented by either a dopamine receptor antagonist, domperidone, or an opiate receptor antagonist, naloxone. These results suggest that xylazine inhibits bovine reticuloruminal motility through its activation of α_2-adrenoceptors, and show that tolazoline can be used as a specific antagonist of xylazine in studies of the α-adrenergic influence on reticuloruminal motility in cattle.

RÉSUMÉ

L'injection intraveineuse d'une dose standard de 0,05 mg/kg de xylazine inhiba la motilité du réseau et du rumen, chez des bovins. L'injection préalable d'antagonistes des récepteurs adrénergiques, capables d'inhiber les récepteurs adrénergiques α_2, à savoir: 0,5 mg/kg de tolazoline et 0,2 mg/kg de yohimbine, annula l'inertie du réseau et du rumen provoquée par la xylazine. La tolazoline s'avéra plus efficace que la yohimbine, puisque 0,5 mg/kg de yohimbine ne provoqua pas d'effet antagoniste et que 0,2 mg/kg de yohimbine se révéla moins efficace que 0,5 mg/kg de tolazoline. La prazosine, un antagoniste des récepteurs adrénergiques α_1 n'empêcha pas l'inhibition de la mobilité du réseau et du rumen due à la xylazine. L'injection de dompéridone, un antagoniste des récepteurs de la dopamine, et celle de naloxone, un antagoniste des récepteurs d'opiate, ne réussirent pas non plus à empêcher l'inhibition de la motilité du réseau et du rumen due à la xylazine. Les résultats de cette expérience sous-entendent que la xylazine inhibe la motilité du réseau et du rumen, chez les bovins, en activant les récepteurs adrénergiques α_2; ils démontrent aussi la possibilité d'utiliser la tolazoline comme antagoniste spécifique de la xylazine, au cours d'études relatives à l'influence des récepteurs adrénergiques sur la motilité du réseau et du rumen, chez les bovins.

INTRODUCTION

Xylazine hydrochloride is widely used in veterinary medicine as a sedative, analgesic and muscle relaxant agent. In particular, cattle are highly sensitive to xylazine. It is also known that this agent inhibits reticuloruminal motility in cattle (1-3).

Xylazine has been characterized as an agonist for α_2-adrenoceptors (4-11). In fact, various actions of xylazine, e.g. sedation in mice and chickens (8), analgesia in rats and mice (12), inhibition of small intestinal motility in mice (13), hyperglycemia associated with inhibition of insulin release in cattle (14) and emesis in dogs (7), were reported to be antagonized by agents possessing α_2-adrenoceptor blocking activity such as yohimbine, tolazoline, piperoxan and phentolamine (15-18). In these studies, yohimbine was found to be the most effective agent for antagonism of the actions of xylazine. In cattle, however, yohimbine is ineffective in antagonizing xylazine-induced sedation (1), although tolazoline antagonizes xylazine-induced central nervous system (CNS) depression (2,19). As yohimbine is the most effective agent for blocking α_2-adrenoceptors (16,18), its inability to antagonize the xylazine-induced sedation focuses attention on the receptive mechanism of xylazine actions in the bovine CNS. It has been shown that xylazine-induced inhibition of reticular motility in sheep is an effect resulting from the central activity of xylazine (10,20), and so it seems of interest to examine whether the xylazine-induced reticuloruminal amotility in cattle is mediated by α_2-adrenoceptors.

Several attempts have been made to reverse the reticuloruminal amotility in cattle induced by xylazine (1-3). As a result, the xylazine-induced ruminal amotility was reported to be reversed by tolazoline (2,3) and yohimbine (1).

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The xylazine-induced reticular amotility was reported to be reversed by tolazoline (3). More recently, Ruckebusch and Allal (21) reported that the inhibition of bovine reticuloruminal contractions induced by xylazine was reversed by yohimbine and tolazoline. However, the receptor mechanism of the xylazine-induced reticuloruminal amotility in cattle has not been well elucidated.

The present study was conducted to determine whether xylazine-induced inhibition of reticuloruminal motility in cattle is mediated by α_2-adrenoceptors and whether this effect involves other receptor types.

TABLE I. Effects of α-Adrenoceptor, Dopamine and Opiate Receptor Blocking Agents on the Xylazine-induced Inhibition of Ruminal Motility in Cattle

Pretreatment[a]	Dose (mg/kg)	Number of Cows	Duration of Ruminal Amotility (Mean ± SD, Minutes)
None (Control)		5	48.0 ± 12.5
Tolazoline	0.5	6	17.5 ± 10.4[b]
Yohimbine	0.2	5	29.0 ± 2.2[c]
	0.5	6	37.5 ± 12.5
Prazosin	0.5	5	54.0 ± 17.1
Domperidone	0.5	5	69.0 ± 22.7
Naloxone	0.1	5	51.0 ± 13.4

[a]Potential antagonists were injected intravenously ten minutes before the intravenous injection of xylazine (0.05 mg/kg)
[b]$p < 0.01$, [c]$p < 0.05$, when compared to the control group, that received xylazine only

MATERIALS AND METHODS

ANIMALS

Eleven nonlactating cows, ten Holsteins and one Jersey (4 to 11 years of age), weighing from 408 to 611 kg (mean 545 kg ± 63 SD), were used in this study. They were housed indoors at night and kept outdoors during the day, and given a commercial cattle concentrate, hay and water *ad libitum*. The animals were randomly used for each experiment. The same animal was not used repeatedly more than five times. The experiments were performed in a large animal X-ray room with the temperature controlled at 20 ± 1°C. Food and water were withheld during the experiments.

EXPERIMENTAL GROUPS

The animals were used in seven groups of five to six cows each. The groups comprised nonpretreated controls and cows pretreated with yohimbine at 0.2 mg/kg bodyweight (0.04 mL/kg) and 0.5 mg/kg bodyweight (0.07 mL/kg), tolazoline at 0.5 mg/kg (0.025 mL/kg), prazosin at 0.5 mg/kg (0.05 mL/kg), domperidone at 0.5 mg/kg (0.25 mL/kg) and naloxone at 0.1 mg/kg (0.01 mL/kg). Cows in each group received a single intravenous injection of xylazine at the dosage of 0.05 mg/kg bodyweight (0.0025 mL/kg). All the potential antagonists were injected intravenously 10 min before the xylazine administration.

MEASUREMENTS OF RUMINAL AND RETICULAR MOTILITY

Reticular motility was examined by means of right-lateral X-ray fluoroscopy. X-ray exposure was performed continuously for 3 min with a horizontal X-ray beam, at 200 kVP and 4 mAs, with an anode distance of 80 cm. The frequency of biphasic contractions of the reticulum per 3 min was recorded prior to drug administration, and then at 5, 15, 30, 45, 60, 75, 90, 105 and 120 min after the xylazine injection. The duration of reticular amotility (frequency of biphasic contractions, 0 per 3 min) was determined.

Ruminal motility was measured by a stethoscopic method. A stethoscope was attached to the left side of the abdomen. The ruminal sounds were monitored in the intervals between the X-ray exposures. After the xylazine injection, the duration of ruminal amotility (no ruminal sounds per 3 min) was determined.

MEASUREMENT OF SEDATION

Additionally, the duration of sedation was measured in this study. The intravenous injection of xylazine (0.05 mg/kg) induced CNS depression, which was characterized by transient recumbency, knuckling of the fetlock joints, head-down posture, open-limbs and unsteady walking. The duration of xylazine-induced sedation was taken as the time between initial knuckling of the fetlock joints and head-down posture and the time of recovery from all effects described above.

DRUGS USED

The drugs used and their sources were as follows: xylazine hydrochloride (Celactal®, 2% solution; Bayer Japan); yohimbine hydrochloride and naloxone hydrochloride (Sigma, St. Louis, Missouri); prazosin hydrochloride (Tokyo Kasei, Ind. Co. Ltd., Japan); tolazoline hydrochloride (Imidalin®, 2% solution; Yamanouchi Pharmaceutical Co. Ltd., Japan); and domperidone (Nauzelin®, 0.2% solution; Kyowa Hakko Ind. Co. Ltd., Japan). Xylazine, tolazoline and domperidone were used as the undiluted 2%, 2% and 0.2% solutions, respectively. Yohimbine, naloxone and prazosin were dissolved in distilled water. All dosages were calculated on the basis of the drug base weight.

STATISTICAL ANALYSIS

The data were subjected to analysis of variance and Student's *t*-test ($p < 0.05$) (22).

RESULTS

EFFECTS OF α_2-ADRENOCEPTOR, DOPAMINE AND OPIATE RECEPTOR BLOCKING AGENTS ON THE XYLAZINE-INDUCED INHIBITION OF RUMINAL MOTILITY

The results are summarized in Table I. The ruminal sound frequency was approximately 1 per min prior to drug administration. In the control cows, 5 min after the intravenous injection of xylazine (0.05 mg/kg bodyweight) ruminal sounds had disappeared. The mean duration of ruminal amotility was 48 min. Pretreatment with an α_2-blocker, tolazoline (0.5 mg/kg), greatly reduced the duration of ruminal amotility induced by xylazine. A second α_2-blocker, yohimbine, at 0.5 mg/kg did not significantly reduce the duration of xylazine-induced rumen amotility. But, yohimbine at a lower dose (0.2 mg/kg) significantly reduced the xylazine-induced inhibition of ruminal motility. The duration

TABLE II. Effects of α-Adrenoceptor, Dopamine and Opiate Receptor Blocking Agents on the Xylazine-induced Inhibition of Reticular Motility in Cattle

Pretreatment[a]	Dose (mg/kg)	Number of Cows	Duration of Reticular Amotility (Mean ± SD, Minutes)
None (Control)		5	51.0 ± 17.1
Tolazoline	0.5	6	15.0 ± 8.4[b]
Yohimbine	0.2	5	32.0 ± 4.5[c]
	0.5	6	46.2 ± 12.1
Prazosin	0.5	5	57.0 ± 12.5
Domperidone	0.5	5	54.0 ± 13.4
Naloxone	0.1	5	54.0 ± 22.7

[a]Potential antagonists were injected intravenously ten minutes before the intravenous injection of xylazine (0.05 mg/kg)
[b]$p < 0.01$, [c]$p < 0.05$, when compared to the control group, that received xylazine only

of xylazine-induced ruminal amotility was not reduced by an α_1-adrenoceptor antagonist, prazosin (0.5 mg/kg), a dopamine receptor antagonist, domperidone (0.5 mg/kg), or an opiate receptor antagonist, naloxone (0.1 mg/kg).

EFFECTS OF α-ADRENOCEPTOR, DOPAMINE AND OPIATE RECEPTOR BLOCKING AGENTS ON THE XYLAZINE-INDUCED INHIBITION OF RETICULAR MOTILITY

The results are summarized in Table II. Biphasic contractions of the reticulum occurred at a frequency of approximately three per 3 min prior to drug administration. In the control cows, 5 min after the intravenous injection of xylazine (0.05 mg/kg bodyweight) the frequency had decreased to zero per 3 min. The mean duration of reticular amotility was 51 min. Pretreatment with tolazoline (0.5 mg/kg) greatly reduced the duration of reticular amotility. Yohimbine at 0.5 mg/kg did not significantly reduce the xylazine-induced reticular amotility. But, yohimbine at the lower dose (0.2 mg/kg) significantly reduced the duration of xylazine-induced reticular amotility. Prazosin (0.5 mg/kg), domperidone (0.5 mg/kg) and naloxone (0.1 mg/kg) did not affect the xylazine-induced reticular amotility at all.

Table III shows the effects of tolazoline, yohimbine, prazosin, domperidone and naloxone on xylazine-induced sedation. Xylazine alone caused CNS depression, which was characterized by transient recumbency, knuckling of the fetlock joints, head-down posture, open-limbs and unsteady walking. Pretreatment with tolazoline (0.5 mg/kg) completely prevented the xylazine-induced recumbency and reduced the duration of xylazine-induced sedation. In contrast, yohimbine at the doses (0.2 and 0.5 mg/kg) used did not affect the duration of xylazine-induced sedation. Also, the depressant effect of xylazine was not antagonized by prazosin (0.5 mg/kg), domperidone (0.5 mg/kg) or naloxone (0.1 mg/kg).

DISCUSSION

The results of the present study show that a standard dose of xylazine (0.05 mg/kg bodyweight) inhibits reticuloruminal motility in cattle. These findings are in agreement with those previously reported (1-3). In sheep, it has been shown that xylazine inhibits reticular contractions through the activation of α_2-adrenoceptors, because this effect is competitively antagonized by α_2-adrenoceptor antagonists, but not by α_1-adrenoceptor antagonists (10). In that report, intravenous yohimbine at 0.2-0.3 mg/kg and tolazoline at 0.6 mg/kg well antagonized reticular amotility induced by xylazine at 0.4 mg/kg intravenously. Also, yohimbine at 0.25 mg/kg intravenously has been reported to reduce the duration of bovine ruminal amotility induced by xylazine at 0.05 mg/kg intravenously (1). Furthermore, tolazoline at 0.2-1.0 mg/kg intravenously has been reported to reverse the inhibition of bovine reticuloruminal motility induced by xylazine at 0.1 mg/kg intramuscularly (3). Based on these observations, the dosages of α-antagonists were determined in this study. The results of the present study suggest that the xylazine-induced inhibition of bovine reticuloruminal motility is mediated by α_2-adrenoceptors, as (a) an adrenoceptor antagonist showing α_2-blocking activity, yohimbine (16-18) at the low dose (0.2 mg/kg) studied, reduced the xylazine-induced reticuloruminal amotility; (b) another α_2-blocker, tolazoline (6,17,18) at 0.5 mg/kg, greatly reduced the reticuloruminal amotility induced by xylazine; and (c) an adrenoceptor antagonist showing α_1-blocking activity, prazosin (16-18) at 0.5 mg/kg, did not reduce the xylazine-induced inhibition of reticuloruminal motility. The results further support the hypothesis that activation of α_2-adrenoceptors inhibits the cyclical motor activity of the bovine reticulorumen, which was recently reported by Ruckebusch and Allal (21).

The present findings also show that the xylazine-induced reticuloruminal amotility is not mediated by dopamine or opiate receptors, since a dopamine receptor antagonist, domperidone (23) (0.5 mg/kg), and an opiate receptor

TABLE III. Effects of α-Adrenoceptor, Dopamine and Opiate Receptor Blocking Agents on the Xylazine-induced Sedation in Cattle

Pretreatment[a]	Dose (mg/kg)	Number of Cows	Duration of Sedation[b] (Mean ± SD, Minutes)
None (Control)		5	93.0 ± 16.4
Tolazoline	0.5	6	45.0 ± 19.0[c]
Yohimbine	0.2	5	91.6 ± 31.7
	0.5	6	105.3 ± 28.5
Prazosin	0.5	5	105.0 ± 38.2
Domperidone	0.5	5	102.0 ± 16.4
Naloxone	0.1	5	108.0 ± 22.2

[a]Potential antagonists were injected intravenously ten minutes before the intravenous injection of xylazine (0.05 mg/kg)
[b]Time when transient recumbency, knuckling of the fetlock joints, head-down posture, open-limbs and unsteady walking all disappeared after the xylazine injection
[c]$p < 0.01$, when compared to the control group, that received xylazine only

antagonist, naloxone (0.1 mg/kg), failed to reduce the effect of xylazine. However, it has been shown that at the doses used in this study, domperidone completely prevents the inhibition of ruminal motility induced by intravenous apomorphine (0.3 mg/kg) or dopamine (0.02 mg/kg) in goats (24), and naloxone not only antagonizes the morphine-induced ruminal amotility but even stimulates ruminal motility in goats (25).

Extrinsic contraction of the rumen and reticulum in ruminants is under the control of the gastric centre, located in an area of the dorsal vagal nucleus of the medulla oblongata, through the afferent and efferent pathways of the vagal nerves (26,27). The exact site of action of xylazine on the reticuloruminal motility is uncertain. In sheep, the intracerebroventricular administration of xylazine was shown to inhibit reticular contractions (20). In addition, in sheep given xylazine, electrical stimulation of the peripheral end of the vagus was reported to elicit reticular contractions (10). These findings show that xylazine inhibits reticular contractions by acting at the CNS without impairing cholinergic transmission at the peripheral levels. Toutain *et al* (10) obtained evidence that central α_2-adrenoceptors mediate the inhibition of reticular contraction by xylazine in sheep. In addition, the α_2-adrenoceptors have been shown to be located in the CNS, and to be abundant in the dorsal vagal nucleus of the medulla oblongat (28). Furthermore, α-adrenoceptors controlling reticuloruminal motility are located in the CNS (27). These observations and our results strongly suggest that the xylazine-induced inhibition of bovine reticuloruminal motility is mediated by central α_2-adrenoceptors. However, as α-receptors also exist in smooth muscle of the rumen and reticulum (27), the possibility could not be eliminated that peripheral as well as central sites are involved in the depressant effect of xylazine.

In monogastric species, yohimbine seems to be a better antagonist than tolazoline for reversal of various actions of xylazine. For example, xylazine-induced sedation in mice (8), analgesia in rats and mice (12), inhibition of gastrointestinal motility in mice (13) and dogs (29) and emesis in dogs (7), have been shown to be more effectively antagonized by yohimbine than tolazoline. In the present study, however, xylazine-induced hypomotility of the rumen and reticulum was not antagonized by yohimbine at 0.5 mg/kg bodyweight, while tolazoline at the same dose did antagonize the xylazine-induced hypomotility. Furthermore, yohimbine at 0.2 mg/kg reduced the hypomotility induced by xylazine, but the reduction was less than that with tolazoline at 0.5 mg/kg. These findings show that tolazoline is more effective than yohimbine as an antagonist of xylazine-induced reticuloruminal hypomotility in cattle. Also, the antagonism of xylazine-induced hypomotility by tolazoline seems to be clinically important.

Although yohimbine is the most effective drug for blocking α_2-adrenoceptors (16-18), the reason for the ineffectiveness of yohimbine at the high dose in antagonizing the xylazine-induced reticuloruminal amotility is unknown. However, Ruckebusch and Allal (21) recently reported that, although tolazoline and yohimbine both reversed the inhibition of reticuloruminal contractions induced by xylazine in sheep and cattle, only tolazoline was able to antagonize the inhibition of secondary ruminal contractions in sheep and alleviate accumulation of gas in the rumen in cattle, while yohimbine did not show these effects and higher doses of yohimbine further impaired the amount of gas eructated. Furthermore, yohimbine at the doses higher than 0.4 mg/kg *per se* was shown to inhibit the frequency of ruminal contractions with an increase in the lower oesophageal sphincter pressure and an increase in the intrinsic smooth muscle tone of the reticulum in cattle (21). Thus, the ineffectiveness of yohimbine at the high dose (0.5 mg/kg) in antagonizing xylazine-induced reticuloruminal hypomotility observed in this study, in part, might be due to the nonalleviation of the accumulation of gas resulting from inhibition of the secondary ruminal contractions and the increase in the intrinsic smooth muscle tone of the reticulum by yohimbine. The results of the present study also show that xylazine-induced sedation is antagonized by tolazoline but not by yohimbine, and these findings are in agreement with those previously reported (1,2,19). The ineffectiveness of yohimbine in blocking the xylazine-induced sedation, in part, could explain the fact that the antagonism of xylazine-induced hypomotility by yohimbine is lower than that by tolazoline, since reticuloruminal motility is inhibited by a reduction in the net excitatory drive to the gastric centre through depression of the central neuronal circuit (27). On the other hand, yohimbine may affect serotonergic, cholinergic, dopaminergic and GABA receptor-related mechanisms, and may exhibit various actions such as a local anesthetic effect, acetylcholinesterase inhibition or monoamine oxidase inhibition (30), suggesting that potential actions of yohimbine other than the blockading of α_2-adrenoceptors may interfere with the reversal of the reticuloruminal hypomotility induced by xylazine in cattle. Also, it was recently reported that subtypes of α_2-adrenoceptors having different neuronal locations, functions and pharmacological properties may exist in the rat brain (31), and so it is possible that the differences between yohimbine and tolazoline in antagonism of the xylazine-induced hypomotility in cattle may be due to the existence of such subtypes of α_2-adrenoceptors.

In conclusion, the results of this study suggest that xylazine-induced reticuloruminal amotility in cattle is mediated by α_2-adrenoceptors. This effect does not appear to involve α_1-adrenergic, dopamingeric or opiate pathways. The present results also indicate that tolazoline can be used as a specific antagonist of xylazine in studies on the α-adrenergic influence on reticuloruminal motility in cattle, and it can be used clinically for the treatment of xylazine-induced hypomotility and bloating in cattle.

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