Antagonistic Effects of Atipamezole on Medetomidine-Induced Sedation in Horses

Kazuto YAMASHITA, Kasumi YONEZAWA, Yasuharu IZUMISAWA, and Tadao KOTANI
Department of Veterinary Surgery I, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu , Hokkaido 069, Japan
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ABSTRACT. The antagonistic effects of atipamezole (20, 40, 60, 80, and 100 μg/kg IV) on medetomidine (10 μg/kg IV)-induced sedation were evaluated in horses. Although 20 and 40 μg/kg of atipamezole were not sufficient to reverse the sedation, 60 μg/kg did effectively reverse the sedation. Atipamezole at 80 μg/kg was more potent, and significantly shortened the duration of sedation without any apparent side effects, but a higher dose of 100 μg/kg was not more effective than 80 μg/kg. The possible use of atipamezole as a reversal agent may enhance the value and availability of medetomidine as a chemical restraint agent in horses. — KEY WORDS: atipamezole, equine, medetomidine.

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The α2-adrenoceptor agonists, initially xylazine, and more recently detomidine, have been widely used in equine practice as analgesics and sedatives to treat colic or injury, and as premedicants for general anesthesia [2, 4, 10]. Medetomidine is more specific in α2-adrenoceptor binding than detomidine and xylazine [12], and is more potent than detomidine in both its behavioural and neurochemical effects [9]. An intravenous injection (IV) of medetomidine at 10 μg/kg produced a similar sedative effect to that of xylazine at 1.0 mg/kg IV, but produced more severe and prolonged ataxia in horses [1, 13]. In clinical practice, care must be taken when medetomidine is used at 10 μg/kg IV due to the possibility of severe ataxia, particularly from 15 to 30 min after the administration [1, 5, 13].

The central and peripheral effects of the α2-adrenoceptor agonists can be reversed by the use of equally specific antagonists. Of these, the most extensively studied has been yohinbine, but new and more potent compounds have been developed recently. Atipamezole, which is a specific antagonist of medetomidine, has been employed in a number of species to reverse the sedative effects of α2-adrenoceptor agonists [3, 4, 6–8, 11]. For example, it has been used to reverse the effects of medetomidine and xylazine in dogs [3, 7] and of xylazine and medetomidine in non-domestic species [6]. In horses, atipamezole at 150 μg/kg IV antagonized sedation induced by 1.0 mg/kg IV of xylazine [8], and at 240 μg/kg IV antagonized sedation induced by 30 μg/kg IV of detomidine [11]. To the best of our knowledge, however, there have been no reports on the antagonistic effects of atipamezole on sedation induced by medetomidine in horses.

The purpose of this study was to investigate and compare the antagonistic effect of atipamezole at various intravenous doses (20, 40, 60, 80, and 100 μg/kg) on severe sedation and ataxia induced by medetomidine at 10 μg/kg IV for clinical applications in horses.

Thirty experiments were performed using nine clinically healthy thoroughbred horses (5 geldings and 4 female horses) with an average body weight of 483 kg (390–566 kg) and an average age of 5.2 years (2–12 years old). No restrictions were placed on the amount of hay and water given to the horses before the experiments. The following drugs were administered to the horses at intervals of at least 6 days: 10 μg/kg medetomidine alone (Domitor®: Meiji Seika Ltd., Tokyo) (group A, n=5), and with 20 μg/kg atipamezole (Antisedan®: Meiji Seika Ltd.) (group B, n=5), 40 μg/kg atipamezole (group C, n=5), 60 μg/kg atipamezole (group D, n=5), 80 μg/kg atipamezole (group E, n=5), or 100 μg/kg atipamezole (group F, n=5) injected 15 min after medetomidine administration. All drugs were administered intravenously through the jugular vein.

The experiments were performed in a quiet room with the temperature at around 20°C. The horses were restrained in wooden stocks and were continously monitored for 120 min after the administration of medetomidine. The degree of sedation in the horses was assessed by measuring the following variables according to the method of Bryant *et al.* [1]. The height of the horse's head was measured as the distance from the floor to the animal's muzzle. The position of the muzzle was marked on the stocks and the height of the mark was measured without disturbing the horse. The degree of ataxia was scored on a subjective scale from 0 to 3. A score of 0 indicated that there was no change from an unsedated animal, a score of 1 indicated that the animal was stable but swaying slightly, a score of 2 indicated that it was swaying and leaning on the stocks, and a score of 3 indicated that it was leaning on the stocks, swaying with its hindlimbs crossed and its forelimbs buckling at the knees. Five stimuli were applied and scored according to the animal's response. A score of 0 was assigned for no response to a stimulus, a score of 1 for a slow hesitant response, a score of 2 for a medium speed response and a score of 3 for a rapid response. The five stimuli included touching the inside of the pinnae with a finger, and touching the coronet of a front and hind foot with the tip of a pen, clapping the hands behind the animal, and waving a piece of cloth in front of the animal's head.

Heart rate (HR), respiratory rate (RR), and body temperature (BT) were measured before and after the administration of medetomidine. HR was monitored by an electrocardiogram (ECG) (Heart Scope 2E16C, NEC Sanei Ltd., Japan) using an A-B lead or a stethoscope, and BT (rectal temperature) was monitored by a thermometer (CTM-303, Terumo, Japan).

These variables were assesed in all groups before the administration of medetomidine, and then at 15, 30, 45, 60, 90, and 120 min of post-administration. The variables were also assesed at 5 and 10 min after the administration of atipamezole in groups B, C, D, E, and F. All visible side effects were recorded.

Analysis of variance (ANOVA) was used in each group to assess changes in HR, RR, BT, and the height of head in each group, and then the differences among the groups were compared by a post-hoc test using the Fisher's PLSD method. The differences between the scored variables of groups were statistically analyzed by the Kruskal-Wallis test and the Mann-Whitney U test. Differences were considered to be significant when $p<0.05$.

Sedation was induced quickly, following the administration of medetomidine. Deep sedation and severe ataxia were observed in all horses at 15 min after the administration of medetomidine (Fig. 1). The horses in group A showed typical sedative conditions up to 60 min post-administration; moderate to severe ataxia and clear decreases in response to the five stimuli and the height of head. These sedative conditions agreed with those reported in previous studies [1, 5, 13].

Atipamezole at 60, 80, and 100 μg/kg IV effectively reversed the sedative effects of medetomidine without any apparent side effects. The ataxia score was reversed dramatically within 10 min after the administration of atipamezole and returned to 0 at 60 min in most horses in groups E and F (Fig. 1a). In group D, the ataxia score was reversed effectively but the change in the score was slow at and after 30 min. No changes in the ataxia score were seen in the horses in groups B and C. The horses in group F showed a significant decrease in the ataxia scores at 60 min compared with those for horses in group A ($p=0.017$).

The total stimuli score also dramatically returned to pre-administration value within 15 min after the administration of atipamezole in most horses in groups E and F (Fig. 1b). Although the total stimuli score was reversed effectively in the horses in groups C and D, a longer time was needed for the total score to return to the pre-administration value. No changes in the total stimuli score were seen in the horses in group B. The horses in group D showed a significant increase in the total stimuli scores at 30 min compared with those for horses in group A ($p=0.018$). The horses in group E showed significant increases in the score at 30 ($p=0.006$), 45 ($p=0.005$), and 60 min ($p=0.018$). The horses in group F showed significant increases in the score at 30 ($p=0.008$) and 45 min ($p=0.011$).

Head height returned to about 60% of the pre-administratin value within 10 min after the administration of atipamezole in groups D, E, and F (Fig. 1c). The horses in group C showed a mild increase in head height. No changes in head height were seen in the horses in group B.

Table 1 shows the effects of atipamezole on HR, RR and BT in horses sedated by medetomidine. Fifteen min after administration of medetomidine, HR decreased to approximately 60% of the baseline values. A-V blocks were observed temporarily after the administration of medetomidine but disappeared before the administration of atipamezole. HR returned to the baseline value after the administration of atipamezole in all groups. However, this reversal only lasted for a short duration , and HR decreased again. The same trend was observed in xylazine [8] and detomidine [11]. HR was approximately 70% of the baseline value at 5 min after the administration of atipamezole and gradually returned to the baseline value in all doses of atipamezole. There was no statistical difference between group A and the other groups. RR decreased to approximately 80% of the baseline value after administration of medetomidine. Atipamezole did not reverse the decrease in RR. BT showed no apparent change in all groups.

The results of the present experiments show that atipamezole at 80 μg/kg IV, 8 times the dose of

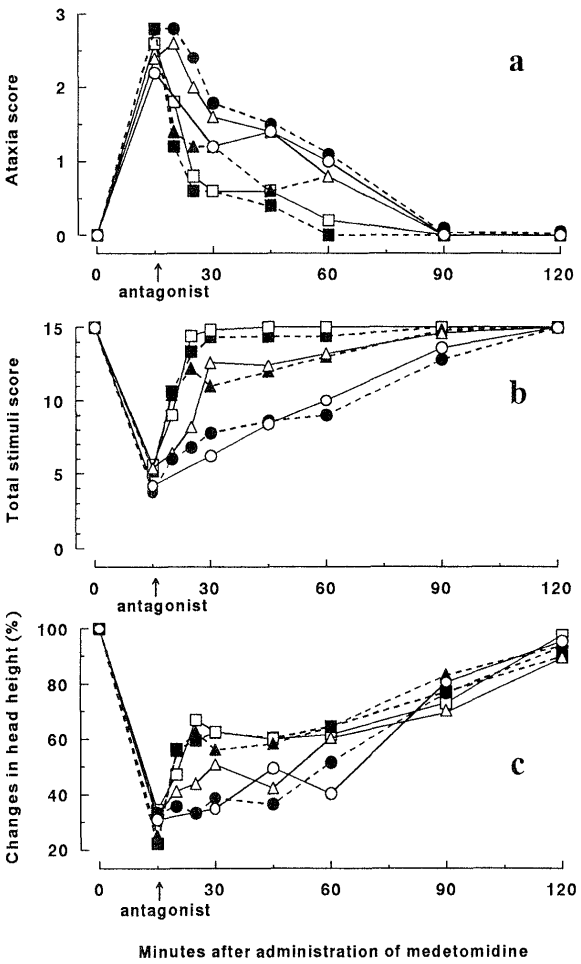

Fig. 1. Effects of atipamezole on ataxia (a; maximum score=3), 5 stimuli (b; full marks=15), and head height in horses sedated by medetomidine. Medetomidine (10 μg/kg) was injected intravenously at 0 min. Atipamezole was injected 15 min after administration of medetomidine (↑). Horses were intravenously administered atipamezole at 20 μg/kg (group B; ●), 40 μg/kg (group C; △), 60 μg/kg (group D; ▲), 80 μg/kg (group E; □), or 100 μg/kg (group F; ■) intravenously, or untreated as a control (group A; ○). Each symbol represents the mean values of all horses (n=5).

Table 1. Changes in heart rate (HR), respiratory rate (RR), and body temperature (BT) in atipamezole-treated and nontreated horses after administration of medetomidine

	Time after the adminisration of medetomidine (min)								
	0	15	20	25	30	45	60	90	120
HR (beats/min)									
A	46 ± 6	28 ± 3	–	–	30 ± 5	33 ± 6	33 ± 5	39 ± 10	41 ± 14
B	43 ± 4	27 ± 7	30 ± 8	34 ± 8	34 ± 9	35 ± 7	36 ± 2	36 ± 4	40 ± 12
C	45 ± 11	27 ± 5	32 ± 10	29 ± 1	30 ± 2	29 ± 4	35 ± 5	31 ± 6	36 ± 6
D	40 ± 6	24 ± 5	29 ± 2	30 ± 6	29 ± 7	30 ± 6	35 ± 7	38 ± 3	43 ± 8
E	45 ± 7	29 ± 5	31 ± 4	35 ± 5	34 ± 6	34 ± 8	36 ± 6	34 ± 5	34 ± 7
F	40 ± 5	28 ± 6	30 ± 8	30 ± 9	32 ± 10	32 ± 8	33 ± 8	34 ± 5	34 ± 5
RR (breaths/min)									
A	22 ± 13	16 ± 5	–	–	12 ± 4	13 ± 4	12 ± 2	13 ± 3	15 ± 2
B	17 ± 5	14 ± 4	13 ± 3	13 ± 4	12 ± 1	11 ± 2	11 ± 3	13 ± 2	12 ± 3
C	20 ± 9	15 ± 3	13 ± 7	12 ± 5	11 ± 3	10 ± 2	10 ± 2	11 ± 3	12 ± 1
D	18 ± 1	14 ± 2	14 ± 2	14 ± 2	14 ± 2	14 ± 2	14 ± 2	14 ± 3	14 ± 4
E	20 ± 1	13 ± 2	12 ± 2	14 ± 2	11 ± 2	12 ± 1	11 ± 2	12 ± 2	13 ± 3
F	17 ± 4	14 ± 3	14 ± 4	14 ± 2	12 ± 2	12 ± 1	14 ± 2	13 ± 2	13 ± 2
BT (°C)									
A	37.8 ± 0.4	37.7 ± 0.5	–	–	37.5 ± 0.6	37.6 ± 0.5	37.6 ± 0.4	37.7 ± 0.4	37.8 ± 0.4
B	38.0 ± 0.3	37.9 ± 0.3	37.9 ± 0.3	37.7 ± 0.4	37.7 ± 0.4	37.7 ± 0.3	37.6 ± 0.2	37.6 ± 0.2	37.7 ± 0.2
C	37.8 ± 0.2	37.3 ± 0.7	37.4 ± 0.8	37.3 ± 0.6	37.4 ± 0.5	37.4 ± 0.5	37.3 ± 0.6	37.3 ± 0.6	37.4 ± 0.5
D	38.0 ± 0.4	38.0 ± 0.6	38.1 ± 0.6	37.8 ± 0.6	37.9 ± 0.6	37.8 ± 0.7	37.7 ± 0.7	37.4 ± 0.8	37.5 ± 0.6
E	38.1 ± 0.3	37.9 ± 0.4	37.8 ± 0.4	37.9 ± 0.3	38.0 ± 0.1	37.8 ± 0.2	37.8 ± 0.3	37.8 ± 0.3	37.7 ± 0.3
F	37.7 ± 0.4	37.9 ± 0.5	37.9 ± 0.4	37.9 ± 0.4	37.8 ± 0.3	37.7 ± 0.3	37.6 ± 0.3	37.5 ± 0.3	37.5 ± 0.4

Horses were treated by an intravenous injection of medetomidine at 10 μg/kg (group A as a control, n=5), medetomidine at 10 μg/kg followed 15 min later by an intravenous injection of atipamezole at 20 μg/kg (B, n=5), 40 μg/kg (C, n=5), 60 μg/kg (D, n=5), 80 μg/kg (E, n=5), and 100 μg/kg (F, n=5). –: Not recorded.

medetomidine, was necessary to reverse sedation induced by medetomidine at 10 μg/kg IV. A higher dose of 100 μg/kg IV was not more effective than 80 μg/kg IV, a dose of 60 μg/kg IV was also effective but was not sufficient to reverse the ataxia induced by medetomidine. In clinical practice, atipamezole is necessary for antagonizing overdose and prolonged sedation of α2-adrenoceptor agonists in horses. If the α2-agonists are overdosed, the horses show severe ataxia and a rapid reversal is required. In the case of medetomidine, atipamezole at 8 times the dose of medetomidine is recommended for reversal.

Atipamezole is a highly selective and specific α2-adrenoceptor antagonist in many species [3, 6, 7]. In ponies, Luna *et al.* [8] reported that sedation induced by 1.0 mg/kg IV of xylazine was effectively reversed by atipamezole at 150 μg/kg IV administered 15 min after xylazine. In horses, Nilsfors and Kvart [11] reported that sedation induced by 30 μg/kg IV of detomidine was effectively reversed by atipamezole at 240 μg/kg IV administered 20 min after detomidine. In the present study, the sedative effects of medetomidine at 10 μg/kg IV were adequately reversed when 80 μg/kg IV of atipamezole was administered 15 min after medetomidine. The sedative conditions in the present study when atipamezole was administered were very similar to those reported by Luna *et al.* [8], and Nilsfors and Kvart [11]. Although simple comparisons are difficult due to differences in the experimental animals and experimental situations, the amount of atipamezole required to reverse sedation induced by medetomidine may be less than xylazine or detomidine, the difference in this dose requirement may reflect the difference in α2: α1-adrenoceptor selectivity ratio between medetomidine and xylazine or detomidine [9].

In conclusion, the sedative effects induced by medetomidine can be reversed quickly and smoothly by atipamezole, and 80 μg/kg of atipamezole, 8 times the dose of medetomidine, is thought to be sufficient to antagonize sedation induced by 10 μg/kg of medetomidine in horses.

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