Assessment of the Sedative Effect of Medetomidine and Determination of Its Optimal Dose in Thoroughbred Horses

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ABSTRACT. The present study was carried out to assessing the sedative effect of medetomidine and determining its optimal dose in thoroughbred horses. Excessive ataxia after sedative treatment is dangerous for horses. Therefore three doses which may cause sufficient sedation with only mild ataxia were examined. Response to stimulation and the severity of ataxia suggested that 7.5 $\mu\text{g/kg}$ BW, i.v., is optimal.—**KEY WORDS:** equine, medetomidine, optimal dose.

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Retention by drugs—sedatives and analgesics—is a procedure of growing need in various treatments in the veterinary field. In particular, drug retention in horses is often required to ensure the safety of both the horse and the person who treats it. The sedation in a standing position is required for horses, so that we necessitate sufficient sedation not to get severe ataxia. Administration of xylazine not combined with other drugs is now used widely for this purpose at the time of various treatments [3]. In thoroughbred horses, however, excitation and dysphoria following xylazine administration, which is not the case in other breeds of horses have been observed [3, 9]. Detomidine has recently become commonly used in horses in the veterinary clinical setting in overseas countries, and its usefulness has been reported in the literature [2, 4]. However, this drug is not commercially available in Japan.

Recent years have seen the advent of a newly developed sedative, medetomidine [4-(1-(2,3-dimethyl)phenyl)-1H-imidazole], which has higher selectivity for the α_2 -adrenoceptor and higher dose dependency than xylazine or detomidine [7]. This drug has been used clinically in dogs [11], cats [10], pigs [6] and some other species of animals, and its usefulness has been recognized. With regard to horses, Kamerling *et al.* [5] evaluated the efficacy of medetomidine as a sedative in thoroughbred horses in comparison with detomidine. Bryant *et al.* [1] also compared the sedative effect of medetomidine and that of xylazine, using mainly ponies. As a result of their experiment, medetomidine at 10 $\mu\text{g/kg}$ was similar to 1 mg/kg of xylazine in its sedation effect but produced more severe and more prolonged ataxia, and medetomidine at 5 $\mu\text{g/kg}$ produced less sedation but a similar degree of ataxia to 1 mg/kg of xylazine.

The purpose of this study was to investigate and compare the sedative effect of medetomidine in relation to intravenous dose (5.0, 7.5 and 10.0 $\mu\text{g/kg}$ of body weight) of this drug for clinical application in thoroughbred horses.

Twelve studies were performed on eight thoroughbred horses (three male and five female). The horses averaged 3.3 ± 0.5 years of age and 445.8 ± 28.7 kg in weight. When the same horse was used in more than one study, the second trial was performed after an interval of one week or more. All horses were judged to be healthy by

physical and laboratory examinations. The drug used in this study was medetomidine (Domitor®, Meiji Seika Co., Ltd., Japan). The doses were 10.0 $\mu\text{g/kg}$ of body weight (med₁₀), 7.5 $\mu\text{g/kg}$ (med_{7.5}) and 5.0 $\mu\text{g/kg}$ (med₅). Each group were composed of four horses, and the drugs were injected into the jugular vein. The experiments were performed in wooden stocks in a quiet room with temperature controlled at $20.6 \pm 1.4^\circ\text{C}$ and humidity at $48.0 \pm 5.5\%$. The horses were injected intravenously with 10.0 μg , 7.5 μg or 5.0 μg of medetomidine per kg. The sedative and analgesic effects of the drug were repeatedly assessed before injection and 5, 10, 15, 30, 45, 60, 75 and 90 min after injection. The degree of sedation of the horses was assessed by measuring the following variables. The degree of standing state was scored on a subjective scale from 0 to 4 (Table 1) for assessing the degree of ataxia (ataxia score). The height of the horse's head was measured as the distance from the floor to the horse's muzzle for assessing the sedative and hypnosis effect. The position of the muzzle was marked on the stock and the height of the mark measured, taking care not to disturb the horse. Seven kinds of stimulation were applied and the responses were scored on a subjective scale of 0 to 3 (Table 2) for assessing the analgesic and sedative effect. The horse's responses were assessed by the total of scores for seven kinds of stimulation. The horse's heart rate was measured with a physiograph (M1094A, Yokogawa Hewlett Packard Co., Ltd., Tokyo) with A-B induction. Ataxia score and total response score to seven kinds of stimulation were compared between the regiments using Kruskal-Wallis's non-parametric method and Mann-Whitney test applying with Ryan's procedure. The degree of head height and heart rate were compared between the regiments using ANOVA-multiple method. Values of $P < 0.05$ were considered significant.

Following the intravenous injection of medetomidine at any dose, sedation was smoothly and quickly induced and the horses became ataxic, and drowsy within a few minutes. Urination, sweating, chaliasia of the anus and penile prolapse were commonly observed and with equal frequency after each treatment. However, muscular spasms were not observed. Smooth onset of sedation without excitation was observed within 5 min post-injection in horses administered medetomidine at any dose. The degree of ataxia was significantly greater after a

Table 1. Comparison of degree of ataxia between this report and the report of Bryant *et al.* [1]

Score	This report	The report of Bryant <i>et al.</i>
0	no change from the unsedated horse	no change from the unsedated horse
1	no change from the stabled horse	no change from the stabled horse
2	swaying with hindlimbs crossed	swaying and leaning on the stocks
3	swaying with hindlimbs crossed and either leaning on the stock or forelimbs buckling at the knee	leaning on the stock, swaying with hindlimbs crossed and forelimbs buckling at the knee
4	leaning on the stock, swaying with hindlimbs crossed and forelimbs buckling at the knee	

Table 2. The seven kinds of stimulations and degree of response to them

Stimulation:	Touching the inside of the naris with a finger
	Touching the inside of the pinnae with a finger
	Waving a piece of cloth toward the horse's head
	Touching the coronet of the right front foot
	Touching the coronet of the right hind foot
	Clapping the right hip
	Making a sound in front of the head
Response to stimulation:	
	Score 0: No response
	Score 1: Slow hesitant response
	Score 2: Medium speed response
	Score 3: Rapid response

Table 3. Statistical analysis of the ataxia score between each regiment

Dose (/kg)	Time after administration (min)								
	0	5	10	15	30	45	60	75	90
10.0 μ g	a	a	a	a	a	a	a	a	a
7.5 μ g	a	b	a	b	b	b	b	b	b
5.0 μ g	a	c	b	b	b	b	c	c	b

Data are compared at full term (from 0 to 90 min) using Kruskal-Wallis's non-parametric method and Mann-Whitney test applying with Ryan's procedure. a, b, c: Different characters show the significant difference ($P < 0.05$) at the same time.

dose of med₁₀ than med₅, significantly greater at 5, 10, 60 and 75 min with med_{7.5} than with med₅, and significantly greater at 5 and from 15 to 90 min with med₁₀ than with med_{7.5} (Table 3, Fig. 1). The degree of head height was maximum at 5 min and has been decreased with time with either dose. It was significantly greater from 30 to 90 min with med₁₀ than at the same time with med₅ ($P < 0.05$), significantly greater from 60 to 90 min with med_{7.5} than at the same time with med₅, and significantly greater at 90 min with med₁₀ than at the same time with med_{7.5} (Table 4). The horse's responses to seven kinds of stimulation were significantly greater at 30 and 75 min with med₁₀ and med_{7.5} than at the same time with med₅ (Table 5, Fig. 2). The heart rate was decreased after administration of medetomidine at any dose, but were not significantly different among the treatments (Table 6). The heart rates had almost returned to presedation values within 90 min of the administration of any dose.

Medetomidine shows higher α_2 -adrenoceptor selectivity and higher dose dependency than xylazine or detomidine, and is known to produce a sufficient sedative effect in small animals even when used at a small dose [6, 10, 11]. It is apparent from the reports of Bryant *et al.* [1] and Kamerling *et al.* [5] that there is a sufficient sedative effect when used in horses. For assessment of the sedative effect, we used a modification of the criteria proposed by Bryant *et al.* [1] (Table 1), because our preliminary study revealed that their criteria based on data from ponies were not applicable to similar assessment in thoroughbred horses, in which signs of ataxia are different from those in ponies. More specifically, although a score of 2 or 3 is given basically when the horse leaned against the stock in assessment of ataxia by the method of Bryant *et al.* [1], our preliminary experiment found that thoroughbred horses showed abnormal positions of the fore legs or hind legs

Table 4. Effects of medetomidine on head height (mean $\pm$ SD, cm) in 4 horses of each regiment

Dose (/kg)	Time after administration (min)								
	0	5	10	15	30	45	60	75	90
10.0 μ g	118.3 $\pm$ 2.4 ^{a)}	25.0 $\pm$ 6.5 ^{a)}	27.0 $\pm$ 5.4 ^{a)}	32.3 $\pm$ 4.2 ^{a)}	32.5 $\pm$ 5.3 ^{a)}	47.5 $\pm$ 10.8 ^{a)}	63.3 $\pm$ 9.0 ^{a)}	80.0 $\pm$ 8.7 ^{a)}	97.3 $\pm$ 10.1 ^{a)}
7.5 μ g	119.8 $\pm$ 6.7 ^{a)}	30.7 $\pm$ 20.1 ^{a)}	36.0 $\pm$ 17.6 ^{a)}	41.3 $\pm$ 16.1 ^{a)}	45.0 $\pm$ 17.3 ^{ab)}	56.0 $\pm$ 18.8 ^{ab)}	71.5 $\pm$ 15.3 ^{a)}	88.8 $\pm$ 9.9 ^{a)}	108.7 $\pm$ 3.8 ^{b)}
5.0 μ g	117.7 $\pm$ 6.1 ^{a)}	34.3 $\pm$ 16.1 ^{a)}	39.0 $\pm$ 17.2 ^{a)}	42.2 $\pm$ 17.8 ^{a)}	64.9 $\pm$ 19.1 ^{b)}	78.6 $\pm$ 15.7 ^{b)}	109.2 $\pm$ 1.2 ^{b)}	16.8 $\pm$ 7.5 ^{b)}	116.3 $\pm$ 4.8 ^{b)}

Data are compared at full term (from 0 to 90 min) using ANOVA-multiple method. a), b) Different superscripts show the significant difference ($P < 0.05$) at the same time.

Table 5. Statistical analysis of mean of total response score to seven kinds of stimulation between each regiment

Dose (/kg)	Time after administration (min)								
	0	5	10	15	30	45	60	75	90
10.0 μg		a	a	a	a	a	a	a	a
7.5 μg		a	a	a	a	a	a	a	a
5.0 μg		a	a	a	a	b	b	b	a

Data are compared at full term (from 0 to 90 min) using Kruskal-Wallis's non-parametric method and Mann-Whitney test applying with Ryan's procedure. a, b: Different characters show the significant differences ($P<0.05$) at the same time.

Fig. 1. Changes in mean of ataxia score in 4 horses for given medetomidine at 10.0 (—○—), 7.5 (—△—) and 5.0 (—□—) $\mu\text{g}/\text{kg}$. Vertical lines show SD.

before leaning against the stock. We, also, need sedation in other place than the wooden stock, to apply for clinical application. Because of these, we used the criteria shown in Table 1. Taking into consideration the facts that thoroughbred horses are sensitive to sounds and that transnasal procedures such as endoscopy are often carried out under sedation, we used seven types of stimulation whereas Bryant *et al.* [1] used five types. As a result, our criteria clarified the differences in the ataxic state change-

Fig. 2. Changes in mean of total response score to seven kinds of stimulation in 4 horses for given medetomidine at 10.0 (—○—), 7.5 (—△—) and 5.0 (—□—) $\mu\text{g}/\text{kg}$. Vertical lines show SD.

ing along with the time course after administration among horses given different doses of medetomidine.

Ataxia was relatively severe 5 and 10 min after administration in horses given a dose of 7.5 $\mu\text{g}/\text{kg}$ (med_{7.5}), however, by 15 min or more after administration, the ataxic state had diminished to almost the same level as that in horses given a dose of 5.0 $\mu\text{g}/\text{kg}$ (med₅), with no horses leaning against the stock. The degree of ataxia was significantly greater almost full term after a dose of med₁₀ than med₅ and med_{7.5}. Therefore, in terms and degree of ataxia, a dose of 7.5 $\mu\text{g}/\text{kg}$ or less may be applicable for clinical use.

Head height was found about 2 min after administration, regardless of the dose, practically reaching a peak at 5 min. However, the degree of head height was generally proportional to the dose, presumably reflecting the intensity of the sedative effect. While head height persisted, moist abnormal breath sounds probably derived from the upper airway were heard in all groups of horses, in the same manner as in ponies [1]. This seems to be attributable to congestion and edema in the upper airway resulting from drooping of the head.

The degree of response to stimulation was also proportional to the dose and time after administration.

Table 6. Effects of medetomidine on heart rate (mean $\pm$ SD, beats/min) in 4 horses of each regiment

Dose (/kg)	Time after administration (min)								
	0	5	10	15	30	45	60	75	90
10.0 μ	34.3 $\pm$ 3.3	19.3 $\pm$ 1.5	20.5 $\pm$ 2.1	25.0 $\pm$ 2.5	26.8 $\pm$ 2.3	27.3 $\pm$ 4.3	28.5 $\pm$ 5.1	30.0 $\pm$ 6.0	31.3 $\pm$ 5.2
7.5 μg	32.8 $\pm$ 5.3	21.0 $\pm$ 1.6	24.8 $\pm$ 2.6	24.5 $\pm$ 2.1	25.5 $\pm$ 1.3	27.0 $\pm$ 1.8	29.8 $\pm$ 3.8	32.3 $\pm$ 3.3	31.5 $\pm$ 2.5
5.0 μg	34.0 $\pm$ 3.6	22.3 $\pm$ 4.0	23.3 $\pm$ 4.0	23.7 $\pm$ 3.1	25.7 $\pm$ 3.1	28.0 $\pm$ 1.6	30.7 $\pm$ 3.1	32.7 $\pm$ 1.7	33.7 $\pm$ 3.1

Data are compared at full term (from 0 to 90 min) using ANOVA-multiple method. There are no significant differences between each regiment at the same time.

However, the threshold of response to stimulation lowered in the med₅ group in comparison with the other two groups. This indicates that 7.5 µg/kg is necessary for achieving sufficient sedation. This finding, considered together with the data on ataxia and head height, suggests that this dose level is optimal in thoroughbred horses. However, response to stimulation of the inner part of the pinna persisted and never faded out, as noted in ponies [1]. Therefore, none of the doses examined in the present study are appropriate for a sedative procedure for treatment related to the pinna, and may required combination with the use of twitch.

The heart rate decreased similarly in all groups during the experiment, and grade-2 atrioventricular block tended to appear more frequently and persistently as the dose of medetomidine increased [8]. This suggests circulatory inhibition, which has also been observed in horses given detomidine [2, 4]. Therefore, the use of procedures to minimize such circulatory inhibition should be investigated into consideration when using this drug.

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