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Medetomidine Sedation and Its Antagonism by Yohimbine in Dogs

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Abstract : The purpose of this study was to determine the antagonistic effects of yohimbine on sedation induced in dogs with medetomidine. Six mixed breed dogs were repeatedly used at a 2 weeks withdrawal time in this study. The dogs received 40 μg/kg of medetomidine followed 15 minutes later by 0.2 ml/kg saline solution (group M) or 0.11 mg/kg yohimbine (group MY). All the dogs were examined before and 5, 15, 30, 45, 60, 75, 90, 120 and 150 minutes after the injection of medetomidine, and the induction and recovery times, vital signs, blood biochemistry and anesthetic quality were recorded. There were significant differences in the recovery of anesthesia between the groups. In both groups the heart rate decreased rapidly down to five minutes after the administration of medetomidine. The activity of ALT, AST and the protein concentration did not change significantly in either group and there was no significant difference between them at any time. Response to noise, muscle tone and analgesic score in the MY group at 30 minutes were significantly lower than those of the M group. When recovering from anesthesia, the dogs treated with yohimbine took less time to achieve sternal recumbency and less time to be able to stand and walk. It was concluded that yohimbine reversed effectively medetomidine sedation in dogs.

Key words **:** medetomidine, sedation, yohimbine, antagonism.

Introduction

Medetomidine, a potent and highly specific α_2-adrenoceptor agonist, is often used in veterinary practice as a sedative, analgesic, and muscle relaxant (13). An antidotal procedure for reversal of medetomidine is useful in shortening the recovery period or controlling the excessive or prolonged sedative condition in dogs. Atipamezole has been used as one of the antagonist of medetomidine in veterinary medicine. However, yohimbine is used to reverse the sedative and cardiovascular effects of α_2-agonist and is used primarily to reverse the effects of xylazine in dogs and cats (1). In dogs and cats, medetomidine has been used alone or in combination with butophanol, morphine or tiletamine/zolazepam (8). Currently, yohimbine of α_2-adrenoreceptor antagoinist, which acts as an antagonist of medetomidine, has still reported on using hormone and metabolism, but a clinical study is less clear.

The purpose of this study was to determine the antagonistic effects of yohimbine on sedation induced in dogs with medetomidine. The induction and recovery times, vital signs, blood biochemical values were determined in dogs treated yohimbine after they had been sedated with medetomidine.

Materials and Methods

Animals and treatments

Six mixed breed dogs (4 males and 2 females) were repeatedly used at a 2 weeks withdrawal time in this study. Their mean age was 4.3 years (range 2-6 years) and mean body weight was 3.8 kg (range 2.7-4.6 kg). Food was withheld for 12 hours, and water was withheld for 6 hours before anesthesia.

Mixed breed dogs of both sexes were randomly assigned to one of two groups of six. The dogs in group M received 40 μg/kg of medetomidine (Domitor®, Pfizar, USA) followed 15 minutes later by 0.2 ml/kg saline solution which was the same volume as yohimbine at the dose of 0.11 mg/kg.

The dogs in group MY received the same doses of medetomidine, followed 15 minutes later by 0.11 mg/kg yohimbine (Antagozil®, Troy Laboratories, Australia). Medetomidine were injected into the biceps femoris muscles, and yohimbine and saline solution were injected intravenous via cephalic vein IV catheters. All the dogs were examined before and five, 15, 30, 45, 60, 75, 90, 120 and 150 minutes after the injection of medetomidine, and the induction and recovery times, vital signs, blood biochemistry and anesthetic quality were recorded.

Induction and recovery times

The induction time was recorded as the time from the injection of medetomidine to lateral recumbency. The dogs' recovery was recorded as the times from the injection of medetomidine to when they achieved sternal recumbency, to when they stood up, and to when they were able to walk.

Vital signs

The rectal temperature was measured with a digital thermometer, the heart rate was measured with auscultation and the respiratory rate was measured by observing chest movement.

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Blood biochemistry

Blood samples were collected at each point by venepuncture from a jugular vein and left to coagulate. They were then centrifuged at 650 g for 15 minutes and the serum was separated. The sample analyzed for alkaline phosphatase (ALP), aspartate aminotransferase (AST), glucose and total proteins with an autoanalyzer (Vettest 8008 Blood Chemistry Analyzer; IDEXX, USA).

Scores for immobilization and analgesia

Score of anesthetic effects (sedative score and anesthetic score) were subjectively evaluated every 15 minutes during anesthesia (Table 1). A score was given to each category.

The levels of sedation and analgesia were assessed according to the criteria in Table 1.

Statistical analyses

The data of heart rate, respiratory and rectal temperature were analyzed by one-way analysis of variation and Duncan's multiple comparison procedure, and by paired-*t* test. The P values below 0.05 were considered to be significant.

Results

Induction and recovery times

The dogs in both groups became sedated after the intramuscular injection of medetomidine, and they all became lateral recumbent within 10 minutes without signs of excitement. The induction time was similar in both groups. While recovering from anesthesia, the M group took a mean 44.4 ± 7.27 minutes to achieve sternal recumbency, compared with 17.6 ± 1.14 minutes by the MY group, 72.2 ± 9.55 minutes to stand, compared with 24.0 ± 4.18 minutes by the MY group, and 82.4 ± 10.36 minutes to be able to walk, compared with 25.6 ± 4.22 minutes by the MY group (Table 2). There were significant differences in the recovery of anesthesia between the groups.

Heart rate, respiratory rate and rectal temperature

In both groups the heart rate decreased rapidly down to five minutes after the administration of medetomidine. In the M group, the heart rate decreased significantly within 5 minutes after medetomidine and remained consistently below the baseline for 120 minutes. In the MY group, the heart rate decreased significantly for 15 minutes, but after the administration yohimbine they were higher than baseline (Table 3). The respiratory rate decreased after the administration of medetomidine in both group, but there were no significant differences (Table 3). The rectal temperature decreased after the administration of medetomidine in both group, and it was significantly lower than the baseline at 75, 90, 120 and 180 minutes in the M group (Table 3).

Blood biochemistry

The activity of ALT, AST and the protein concentration did

Table 1. Subjective criteria used to score levels of sedation (spontaneous posture, response to noise, muscle relaxation) and analgesia (pedal withdrawal) in dogs treated with medetomidine

Variable	Score	Criteria
Sedative score		
Spontaneous posture		
	0	Normal
	1	Tired but standing
	2	Lying, able to attain sterna recumbency
	3	Lying, rising with difficulty
	4	Unable to rise
Response to noise (dropping of haemostatic forceps)		
	0	Sensitive or normal
	1	Weak
	2	No reaction
Muscle tone of jaw and tongue		
	0	Normal
	1	Slightly weak, tongue cannot be pulled out, or can be pulled out only with difficulty
	2	Weak, tongue can be pulled out, but the dog is able to withdraw it
	3	Very weak, the tongue can easily be pulled out and the dog is unable to withdraw it
Analgesic score (Pedal withdrawal response to pinching of a digit or interdigital web)		
	0	Hypersensitive or normal
	1	Slightly impaired
	2	Clearly weak
	3	Absent

Table 2. Induction, sternal recumbency, standing and walking times after administration of medetomidine or medetomidine/yohinbine in dogs

	Induction times	Sternal recumbency time	Standing times	Walking times
M	9.6 ± 2.30	44.4 ± 7.27	72.2 ± 9.55	82.4 ± 10.36
MY	10 ± 2.92	17.6 ± 1.14*	24.0 ± 4.18*	25.6 ± 4.22*

Data are expressed as mean ± SD (n = 5). *Significantly different ($P < 0.05$) from the M.
M: medetomidine. MY: medetomidine and yohimbine.

not change significantly in either group and there was no significant difference between them at any time. The glucose concentration was decreased after the induction of anesthesia in both group, but it increased after 75 minutes in the M group and gradually decreased after yohimbine administration in the MY group (Table 4).

Scores of anesthetic effects

Spontaneous posture scores in the M group were significantly decreased at 75 and 90 minutes after drug administration. However, in the MY group, scores of anesthetic effects were significantly decreased at 30 minutes after yohimbine administration (Table 5). Response to noise, muscle tone and analgesic score in the MY group at 30 minutes were significantly lower than those of the M group ($p < 0.05$).

Discussion

Medetomidine is a more selective and full agonist for central α_2-adrenergic receptor than xylazine and detomidine. It is used intramuscularly or intravenously as an analgesic and as a sedative in dogs and cats (13). In dogs and cats, medetomidine has a rapid onset of action and can be administered IV or IM. After IM administration, the drug is rapidly absorbed, and peak plasma concentrations are reached within 30 minutes (12). The elimination half-life of medetomidine (80 μg/kg) after IM administration in dogs is 1.28 hours (12). Elimination occurs mainly by biotransformation in the liver, and inactive metabolites are excreted in the urine. Onset of sedation, analgesia, and muscle relaxation is rapid after IM administration of medetomidine to dogs and cats, and the intensity and duration of these effects depend on dose (10). When medetomidine is given IM to dogs at a dose of 40 μg/kg, significant sedation is apparent within 10 minutes and persists for 44 minutes in this study. The adverse effects reported with medetomidine are essentially extensions of its pharmacologic effects including bradycardia, occasional AV blocks, decreased respiration, hypothermia, urination, vomiting and hyperglycemia.

Yohimbine is used as a selective α_2-receptor antagonist of the sedative and cardiovascular effects of xylazine in dogs, cats, and several exotic species (3). Yohimbine increases heart rate and blood pressure, causes central nervous system (CNS) stimulation and antidiuresis, and has hyperinsulineaemic effects (7). Many reports on a variety of species have documented yohimbine's efficacy in antagonizing the various actions of xylazine. 0.1 mg/kg IV yohimbine reverses the sedative and cardiovascular effects of xylazine (1 mg/kg) when administration IV or IM (4). The action of medetomidine can be reversed by α_2-receptor antagonist, such as the highly specific receptor atipamezole or the less specific yohimbine (9). Although yohimbine is considered to be mainly a α_2-adrenergic receptor blocker, medical applications for medetomidine have not been investigated.

In this study, the MY group recovered more rapidly than the M group, suggesting that the effects of medetomidine were antagonized by yohimbine. Animals given yohimbine (0.11 mg/kg IV) after administration medetomidine (0.04 mg/kg IM), show increases of heart rate and initial signs of arousal within 17 minutes and are walking within 26 minutes. Yohimbine antagonized the hypertension, hypotention and bradicardia induced by α_2-adrenergic agonist in dogs (6). In the present study, the MY group received 0.11 mg/kg yohimbine and had higher heart rates after 30 minutes than the M group.

Yohimbine reversed the respiratory depression induced by xylazine and ketamine (5). In this study, yohimbine showed reversed effects of the respiratory depression induced by medetomidine. The respiratory rate was decreased after the administration of medetomidine in both groups, but increased after the administration of yohimbine in the MY group. The primary disadvantages of medetomidine are bradycardia with heart block and respiratory depression. These side effects are antagonized by yohimbine.

In this study, the rectal temperature of both groups decreased slightly in the first minutes and significantly decreased at the 75, 90, 120 and 180 minutes in the M group after the injection of medetomidine, possibly due to the decreased heart rate. However, after the administration of yohimbine, the rectal temperature in the MY group was not decreased less than the M group, probably as a result of the reversal of the medetomidine-induced effects.

The peak levels of sedation and analgesia occurred between 15 minutes and 30 minutes after intramuscular administration of medetomidine, and the effects were continued on average for approximately 45 minutes in the M group. However, after the administration of yohimbine, the score of anesthetic effects in the MY group was significantly lower than that of the M group.

Yohimbine decreased the plasma concentration of glucose, probably as a result of an increase in plasma insulin concentration. Hsu and others (1987) also observed that yohimbine decreased plasma glucose concentration (7). The dogs received

Table 3. Vital signs (heart rate, respiratory rate and rectal temperature) after administration medetomidine or medetomidine/yohimbine in dogs

	Group	Pre	5 min	15 min	30 min	45 min	60 min	75 min	90 min	120 min	180 min
HR (beats/min)	M	115.4 ± 32.6	50.2 ± 16.2*	45.4 ± 12.1*	41.8 ± 8.1*	47.4 ± 16.4*	47.8 ± 17.7*	52.8 ± 13.5*	56.6 ± 8.0*	62.2 ± 11.5*	81.2 ± 7.4
	MY	108.2 ± 5.5	47.4 ± 9.7*	47.0 ± 11.3*	118.8 ± 14.3	N.E	N.E	N.E	N.E	N.E	N.E
RR (breaths/min)	M	31.2 ± 6.1	21.2 ± 6.9	21.4 ± 9.3	17.2 ± 7.1	20.4 ± 9.8	28.4 ± 18.4	22.4 ± 9.7	18.6 ± 7.5	21.2 ± 8.2	25.4 ± 5.9
	MY	30.6 ± 5.0	22.0 ± 4.2	22.8 ± 10.3	31.6 ± 6.1	N.E	N.E	N.E	N.E	N.E	N.E
RT (°C)	M	39.0 ± 0.4	38.9 ± 0.3	38.6 ± 0.4	38.0 ± 0.5	37.9 ± 0.6	37.5 ± 0.6	37.0 ± 0.8*	36.9 ± 0.8*	37.0 ± 0.7*	37.0 ± 0.6*
	MY	39.0 ± 0.4	38.9 ± 0.4	38.9 ± 0.4	38.9 ± 0.4	N.E	N.E	N.E	N.E	N.E	N.E

Data are expressed as mean ± SD (n = 5), *Significantly different from the baseline ($P < 0.05$)
N.E: Not examined, M: medetomidine, MY: medetomidine and yohimbine

Table 4. Blood chemical values after administration of medetomidine or medetomidine/yohimbine in dogs

	Group	Pre	45 min	75 min	180 min
Glucose (mg/dl)	M	85.2 ± 20.1	66.4 ± 24.1	95.0 ± 48.0	112.6 ± 21.5
	MY	77.8 ± 28.3	61.0 ± 20.7	58.0 ± 10.7	57.0 ± 20.7
Total protein (g/dl)	M	6.0 ± 0.9	6.0 ± 0.9	6.6 ± 1.6	6.6 ± 0.9
	MY	6.0 ± 0.5	5.9 ± 0.4	6.0 ± 0.9	6.0 ± 0.9
ALT (U/l)	M	36.6 ± 7.0	40.0 ± 12.1	40.8 ± 12.8	42.4 ± 7.7
	MY	35.4 ± 12.9	35.2 ± 11.8	35.4 ± 12.9	35.4 ± 12.9
AST (U/l)	M	28.0 ± 10.3	25.8 ± 8.1	26.2 ± 8.3	26.8 ± 12.6
	MY	26.6 ± 13.2	30.8 ± 19.9	25.8 ± 8.1	25.8 ± 8.1

Data are expressed as mean ± SD (n = 5), M: medetomidine, MY: medetomidine and yohimbine

Table 5. Score of anesthetic effects (spontaneous posture, response to noise, muscle tone and analgesic score) after administration of medetomidine or medetomidine/yohimbine in dogs

Effect	Group	5 min	15 min	30 min	45 min	60 min	75 min	90 min	120 min
Spontaneous posture	M	3.4 ± 0.89	3.8 ± 0.45	4.0 ± 0.0	3.2 ± 1.10	1.6 ± 0.89	1.4 ± 1.14+	0.4 ± 0.55+	0.0 ± 0.0+
	MY	3.2 ± 0.45	3.8 ± 0.45	0.0 ± 0.0+	N.E	N.E	N.E	N.E	N.E
Response to noise	M	1.6 ± 0.55	1.8 ± 0.45	2.2 ± 0.45	2.0 ± 0.71	1.0 ± 0.71	0.6 ± 0.55	0.6 ± 0.55	0.0 ± 0.0+
	MY	1.6 ± 0.55	2.0 ± 0.0	0.0 ± 0.0+	N.E	N.E	N.E	N.E	N.E
Muscle tone	M	1.6 ± 1.35	2.4 ± 0.89	2.8 ± 0.45	1.4 ± 0.89	0.8 ± 0.84	0.4 ± 0.55	0.0 ± 0.0	0.0 ± 0.0
	MY	2.0 ± 1.00	2.2 ± 1.30	0.0 ± 0.0+	N.E	N.E	N.E	N.E	N.E
Analgesic score	M	1.8 ± 1.30	2.2 ± 1.10	1.6 ± 0.89	1.0 ± 0.71	0.4 ± 0.55	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	MY	2.2 ± 1.10	2.6 ± 0.55	0.0 ± 0.0+	N.E	N.E	N.E	N.E	N.E

Data are expressed as mean ± SD (n = 5), +Significantly different from the baseline ($p < 0.05$)
N.E: Not examined, M: medetomidine, MY: medetomidine and yohimbine

a low dose of yohimbine, which resulted in an increase in their respiratory rate and heart rate. Yohimbine may cause transient apprehension or CNS excitement, muscle tremors, salivation, increased respiratory rates and hyperemic mucous membranes (11), but the adverse effects were not observed in this study, probably owing to differences in the volume and timing of the dose administration. The hypertensive, hypotensive, and cardiac slowing action of IV xylazine (1 mg/kg) are antagonized in the dog by an IV dose of 0.1 mg/kg yohimbine (2). In this study, IM medetomidine (0.04 mg/kg) can be antagonized rapidly and completely by an IV dose of 0.011 mg/kg yohimbine.

In conclusion, the administration of yohimbine (0.11 mg/kg) effectively reversed medetomidine (0.04 mg/kg) - induced sedation in dogs. The action of reversing was seen within 15 minutes. Recovery from sedation was quick and smooth, and minimal adverse effects were seen in the MY group.

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개에서 Medetomidine 진정에 대한 Yohimbine의 길항작용

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요 약 : 이 연구의 목적은 개에 있어서 medetomidine에 대한 yohimbine의 길항효과를 알아 보는데 있다. 총 6 마리의 잡종견 (수: 4 마리, 암: 2 마리)을 본 연구에 2주일의 휴약기간을 두고 반복실험을 하였다. 개들의 평균 연령은 4.3세 (2-6세) 이였고, 평균체중은 3.8 kg (2.7-4.6 kg) 이였다. 그룹 M은 대조군으로서 medetomidine을 40 μg/kg 용량으로 근육 내 투여하고 15분 후에 saline을 0.2 ml/kg 용량을 정맥 내로 투여하였다. 그룹 MY는 실험 군으로서 medetomidine을 40 μg/kg 용량으로 근육 내 투여하고 15분 후에 yohimbine을 0.11 ml/kg 용량을 정맥 내로 투여하였다. 마취시간에 대한 평가로 induction time, sternal time, standing time과 walking time을 측정하였다. Vital signs으로서 심박동수, 호흡수와 직장체온을 측정하였으며, 혈액화학 치로서 glucose, total protein, ALT와 AST를 측정하였다. 실험결과, medetomidine 투여 후 서맥과 호흡저하를 보였으나, yohimbine 투여 후에는 심박수의 증가와 호흡수의 증가를 나타냄으로써 yohimbine이 medetomine으로 유발된 호흡저하와 서맥을 길항하는 효과를 나타내었다. Medetomine 투약 후 yohimbine을 투여한 군에서는 대조군에 비하여 흉와시간, 기립시간과 보행시간을 현저히 단축시키는 영향을 나타내었다. 결론적으로 개에서 yohimbine은 medetomidine에 대한 양호한 길항작용을 나타내었다.

주요어 : medetomidine, 진정, yohimbine, 길항작용