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Antiemetic Effect of Dexamethasone in Dogs Sedated with Medetomidine

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Abstract : Antiemetic effect of dexamethasone in dogs sedated with medetomidine was evaluated. On the day of experiment, five minutes prior to medetomidine (40 μg/kg, IM) injection, dexamethasone was administered intravenously at the doses of 0.25, 0.5 and 1.0 mg/kg. Control group was received at 0.1 ml/kg of saline instead of dexamethasone. The dose of 0.5 and 1.0 mg/kg of dexamethasone significantly reduced emetic episode. The degree of sedation determined by visual sedation scoring was not influenced by dexamethasone pretreatments. In addition, the values of complete blood counts and blood chemistry did not show significant changes and were within normal ranges before and the day after experiment. These results show that the doses of 0.5 and 1.0 mg/kg of dexamethasone are useful and safe method to prevent emetic episode inducing by medetomidine in dogs, without evidence of any clinically relevant influences.

Key words **:** dexamethasone, medetomidine, antiemetic effect, dog.

Introduction

Medetomidine [4-(1-(2,3-dimethylphenyl)ethyl)-1H-imidazole] is a commonly used sedative analgesic and preanesthetic in veterinary medicine (6,21,22), and when it used with barbiturates, ketamine, or inhalation anesthetics, it produces safe and reliable degree of sedation, muscle relaxation, and analgesia (21). Its efficacy is more potent than other α_2-adrenoceptor agonists (5). Especially, availability of a selective antagonist, atipamezole, makes medetomidine to be a useful chemical sedatives for medical treatments like ear flushing, radiological and ultrasonographical examination, catheterization, and other light manipulations. But medetomidine also has adverse effect including vomiting like other α_2-adrenoceptor agonists (17). Vomiting rate comes up to 30% (5), and it may occur with the earliest signs of sedation following administration (23). Perioperative vomiting may increase the risk of aspiration pneumonia, delay a surgical time and cause a surgical field or a residence contamination. Also, it is an unpleasant episode to animals and owners.

Corticosteroids are usually used to treat allergic and immune-mediated diseases, pruritus, shock states, and the CNS edema (8). In 1981, dexamethasone is presented to be an effective antiemetics in patients treated with chemotherapy (1). From then numerous studies demonstrated that dexamethasone could prevent a nausea and vomiting during chemotherapy for cancer and anesthesia for surgical intervention in human beings and animal models (12,14,16,19).

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There have been, however, no reports to evaluate the efficacy of dexamethasone for preventing medetomidine-induced nausea and vomiting in dogs. Hence, the aim of this study was to evaluate the antiemetic effect of dexamethasone in dogs treated with medetomidine. The effect of dexamethasone on analgesic and sedative efficacy of medetomidine was also evaluated.

Materials and Methods

Animals

Fifty five healthy adult, mixed-breed dogs of either sex, weighing from 2.4 to 6.5 kg (4.32 ± 1.18 kg) were used in this study. They were vaccinated (Vanguard Plus 5CV®, Pfizer Animal Health Korea Ltd., Korea) and dewormed (Rintal Tablet®; Bayer Health Care Ltd., Korea) at least one month before the experiment. A commercial dry pellet food (Biomill®; Woosung Feed Co. Ltd., Korea) and water was always available ad libitium. Dogs were randomly divided into 4 groups; the group treated with 0.1 ml/kg of normal saline and medetomidine (10 dogs, Control group), the group treated with 0.25 mg/kg of dexamethasone and medetomidine (15 dogs, D-0.25 group), the group treated with 0.5 mg/kg of dexamethasone and medetomidine (15 dogs, D-0.50 group), and the group treated with 1.0 mg/kg of dexamethasone and medetomidine (15 dogs, D-1.00 group).

Procedures

Before and one day after experiments, CBC and serum alanine aminotransferase (SALT), serum aspartate aminotransferase (SAST), blood urea nitrogen (BUN), creatinine, and

total protein were measured.

At the day of experiment, about 200 g of food and water were given 2 hours before dexamethasone treatment. In order to stimulate its appetite, about 50 g of a canned meat was mixed to food. Three doses of dexamethasone (Dexamethasone disodium phosphate inj.®; Sinil pharm Ltd., Korea) or normal saline was administered via cephalic vein. Five minutes later, all dogs were given 40 μg/kg of medetomidine (Domitor®; Orion Pharma., Finland) intramuscularly on triceps brachii muscles. From then, antiemetic and sedative effects were evaluated for 60 minutes

Evaluations

Antiemetic effect

(1) Emetic response score: emetic response in each dog was scored as followings; if a dog showed a emetic response, emetic response were scored 1, but if not it was scored 0. Emetic response was characterized by rhythmic abdominal contractions that were either associated with the oral expulsion of solid or liquid material from the gastrointestinal tract (vomiting) or not associated with the passage of material (nausea).

(2) Emesis latency time: time to first onset of emetic response after MED administration was measured.

Degree of sedation

The degree of sedation was measured by Visual Sedation score (VSS) subjectively at 5, 15, 30, 60 minutes after MED administration. VSS in the present study (Table 1) was modified from a sedation index established by Ansah *et al.* (3). For more accuracy, three evaluators participated in scoring, and average of 3 different VSS per dog was obtained. The evaluation was conducted that posture and gait was divided from 0 point to 6, and response to the veterinarian's manipulations was devided from 0 point to 3 (Table 1). Summing these parameters gave the total sedation score (0-9). The degree of response to the veterinarian's manipulations was tested by pinching the interdigital skin of a hind limb.

CBC and blood chemistry

Before and one day after experiments, CBC was measured by an auto blood cell analyzer (HEMA VET 850®; CDC Technologies Inc., USA) and blood chemistry (SALT, SAST, BUN, creatinine, and total protein) was measured by an auto dry chemistry analyzer (SPOTCHEM™ SP-4410®; Kyoto DAIICHI KAGAGU Co. Ltd., Japan).

Data analysis

Statistical analysis was performed by an analysis of variance (ANOVA), with tests for multiple comparisons in SAS program (version 8.1, SAS Institute Inc., USA). Differences at $p < 0.05$ were considered significant.

Results

Emetic response score

The number of dog showing emetic response was 4, 5, 1 and 1 in Control, D-0.25, D-0.50, and D-1.00 group, respectively. Emetic response score was 0.40 ± 0.52, 0.33 ± 0.49, 0.07 ± 0.26, and 0.07 ± 0.26 in Control, D-0.25, D-0.50, and D-1.00 group, respectively. Emetic response score was significantly reduced in D-0.50 and D-1.00 group (Fig 1).

Emesis latency time

Most of the emetic episodes occurred during the initial phases of treatment. Time to first onset of emetic episode was 3.59 ± 0.72 minutes in Control group, 3.35 ± 0.98 minutes in D-0.25 group, 3.78 minutes in D-0.50 group, and 4.35 minutes in D-1.00 group, respectively. However, no significant difference was observed between groups (Fig 2).

Degree of sedation

Intramuscular injection of 40 μg/kg of medetomidine showed moderate to profound sedation. On an average, VSS was highest at 30 minutes in D-1.00 group, and at 15 minutes in the other groups, but significant changes were not found

Table 1. Scoring for sedation in dogs after dexamethasone and medetomidine administration

Posture and gait	
laterally recumbent, seems asleep, and is not easily wakened by light manipulations	6
laterally recumbent and seems asleep but can be wakened easily by light manipulations	5
sternally recumbent, seems awake but unable to rise or does not make attempt to rise, can not lift head up	4
sternally recumbent, can lift head up and hold for a while, occasionally makes weak attempts to rise but unable to rise fully	3
sternally recumbent or able to take sternal or sitting position with slight or no difficulty	2
stands and walks wobbling	1
walks normally	0
Resistance to manipulations	
no resistance to manipulations	3
weak resistance to manipulations	2
moderate or delayed resistance to manipulations	1
strong/fairly strong resistance to manipulations	0

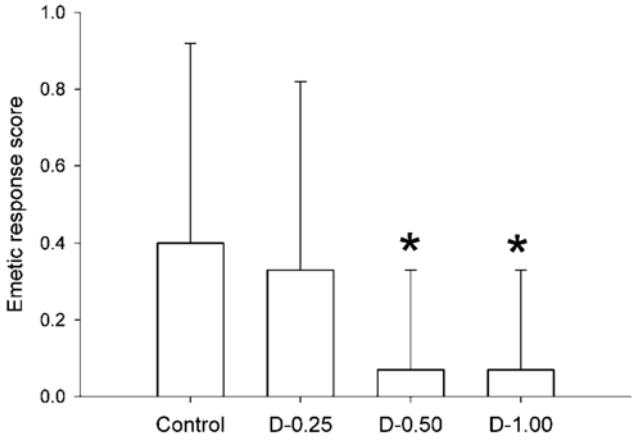

Fig 1. The emetic response score (mean ± SD) in dogs treated with dexamethasone and medetomidine. Five min before medetomidine (40 μg/kg, IM) injection, saline or dexamethasone (0.25, 0.5, 1.0 mg/kg, IV) was administered (group 'Control', 'D-0.25', 'D-0.50', 'D-1.00'). *$p < 0.05$ compared with Control group.

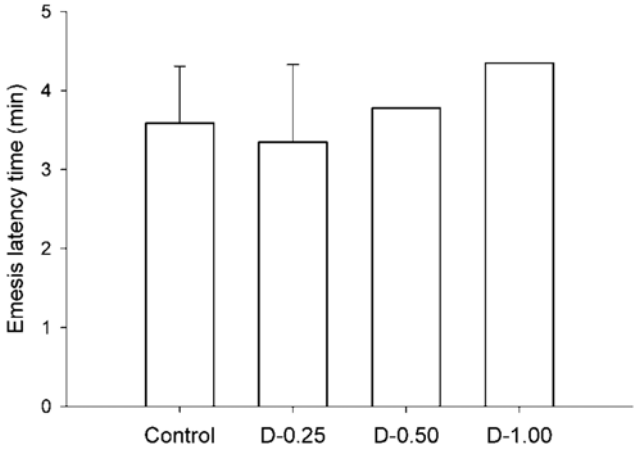

Fig 2. The emesis latency time (mean ± SD) which is time to first onset of emetic response after medetomidine administration in dogs treated with dexamethasone and medetomidine. Five min before medetomidine (40 μg/kg, IM) injection, saline or dexamethasone (0.25, 0.5, 1.0 mg/kg, IV) was administered (group 'Control', 'D-0.25', 'D-0.50', 'D-1.00'). The number of dog showing emetic response was 4, 5, 1 and 1 in Control, D-0.25, D-0.50, and D-1.00 group, respectively.

between Control group and experimental groups (Fig 3).

CBC

The values of WBC, RBC, packed cell volume, and platelet were within normal ranges in all groups (Table 2).

Blood chemistry

The values of SALT, SAST, BUN, creatinine, and total protein were in normal ranges, and were not significantly changed in all groups (Table 3).

Discussion

The present results showed that 0.5 and 1.0 mg/kg of dexamethsone could efficiently reduce emetic episode in dogs treated with medetomidine.

Antiemetic effect of dexamethasone in cats sedated with xylazine was also reported (14). The antiemetic mechanism of action of corticosteroids such as dexamethasone is not well-understood. However, inhibition of a synthesis of prostaglandins (2,4), central or peripheral inhibition of a synthesis of serotonin (9), and changes in the permeability of the blood-brain barrier to serum proteins (15) were suggested for a mechanism.

Dexamethasone pretreatment which of dose was more than 0.5 mg/kg showed significant antiemetic effect compared with saline treatment. In the present study, all dogs were fed food two hours before medetomidine administration for easy induction and confirmation of emesis, and this method increased vomiting rate up to 40% in control group. Dexamethasone pretreatment reduced emesis episode rate down to 7%. In addition, interval of dexamethasone and medetomidine treatment was prefixed just at 5 minutes. Relatively low dose of dexamethasnone and short injection interval of two drugs in the present study were easy for practical application

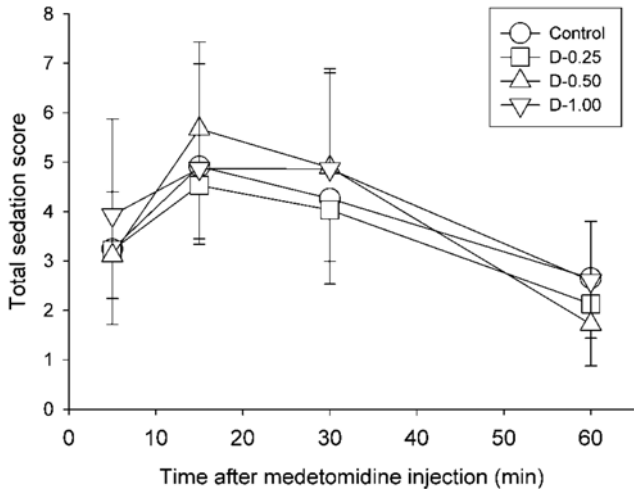

Fig 3. Total sedation score versus time after various doses of dexamethasone and 40 μg/kg of medetomidine administration in dogs. Five min before medetomidine (40 μg/kg, IM) injection, saline or dexamethasone (0.25, 0.5, 1.0 mg/kg, IV) was administered (group 'Control', 'D-0.25', 'D-0.50', 'D-1.00').

in veterinary clinics.

Total sedation scores, CBC and blood chemistry values did not have significant differences, and CBC and blood chemistry values were within normal range. Long-term administration of corticosteroids causes untoward effects which generally are manifested as symptoms of hyperadrenocorticism (8), but a single high dose of dexamethasone is considered safe (11, 13). In addition, there were no reports on adverse effects related to a single dose administration of dexamethasone.

Dopamine receptor antagonists, such as metoclopramide,

Table 2. Values of CBC (mean ± SD) before and one day after injection of saline or dexamethasone (0.25, 0.5, 1.0 mg/kg, IV) and medetomidine (40 μg/kg, IM) in dogs (group 'Control', 'D-0.25', 'D-0.50', 'D-1.00')

Parameters		Control	D-0.25	D-0.50	D-1.00
WBC (K/μl)	Before	12.68 ± 3.62	13.02 ± 3.23	14.04 ± 3.11	12.21 ± 3.23
	After	13.05 ± 2.59	11.89 ± 2.20	13.29 ± 2.97	13.65 ± 2.37
RBC (M/μl)	Before	6.72 ± 1.01	6.75 ± 0.80	7.09 ± 0.72	7.27 ± 0.92
	After	6.98 ± 0.74	6.64 ± 0.79	6.97 ± 0.75	7.32 ± 0.88
PCV (%)	Before	42.31 ± 3.70	43.24 ± 4.17	46.62 ± 5.50	44.63 ± 4.53
	After	43.80 ± 3.92	43.41 ± 4.02	45.94 ± 4.99	44.75 ± 4.57
PLT (K/μl)	Before	403.30 ± 68.70	388.47 ± 77.42	355.33 ± 78.61	385.87 ± 80.08
	After	412.40 ± 69.21	392.20 ± 66.11	364.27 ± 77.29	382.93 ± 81.76

Abbreviations: WBC: white blood cell; RBC, red blood cell; PCV, packed cell volume; PLT, platelet (K/μl)

Table 3. Values of blood chemistry (mean ± SD) before and one day after injection of saline or dexamethasone (0.25, 0.5, 1.0 mg/kg, IV) and medetomidine (40 μg/kg, IM) in dogs (group 'Control', 'D-0.25', 'D-0.50', 'D-1.00')

		Control	D-0.25	D-0.50	D-1.00
SALT (IU/L)	Before	25.00 ± 12.44	21.87 ± 7.51	25.73 ± 9.72	25.87 ± 8.84
	After	23.70 ± 10.27	23.47 ± 6.49	24.40 ± 5.72	26.00 ± 8.18
SAST (IU/L)	Before	16.30 ± 6.04	16.13 ± 4.94	17.07 ± 7.62	17.07 ± 4.91
	After	15.40 ± 4.95	17.20 ± 5.02	16.20 ± 6.18	18.67 ± 5.02
BUN (mg/dl)	Before	13.90 ± 3.63	14.67 ± 3.50	16.53 ± 3.85	14.87 ± 2.61
	After	14.80 ± 3.61	15.27 ± 2.60	17.40 ± 3.46	15.20 ± 3.14
Cre (mg/dl)	Before	0.90 ± 0.23	0.97 ± 0.25	0.99 ± 0.21	1.09 ± 0.21
	After	1.00 ± 0.23	0.89 ± 0.19	1.08 ± 0.25	1.11 ± 0.23
T-pro (g/dl)	Before	5.74 ± 0.70	7.05 ± 0.63	6.47 ± 0.61	6.30 ± 0.58
	After	6.01 ± 0.57	6.83 ± 0.48	6.58 ± 0.58	6.25 ± 0.43

Abbreviations: SALT, serum alanine aminotransferase; SAST, serum aspartate aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; T-pro, total protein

generally are less effective and less selective than the serotonin receptor antagonists and have more adverse effects than other antiemetics (7,10,18). In comparison dopamine receptor antagonists, serotonin receptor antagonists and corticosteroids are regarded as a most effective antiemetics showing few side effects and are convenient to use in human medicine (7). Ondansetron, a selective serotonin receptor antagonist, is a potent antiemetic agent and has less adverse effects than dopamine receptor antagonists. Nevertheless, high costs and no uniform efficacy of serotonin receptor antagonists make the burden for common use (10,20). On the contrary, a prominent characteristic of dexamethasone is cost-effectiveness as well as potent antiemetic agent (19). Therefore, dexamethasone may be a good alternative remedy for the situation of emesis inducing by medetomidine in dogs.

In conclusion, 0.5 or 1.0 mg/kg of dexamethasone administered intravenously 5 minutes before administration of medetomidine significantly decreased emetic episodes induced by medetomidine without compromising sedative effects in dogs. So, dexamethasone pretreatment may be useful as an antiemetic agent in dogs sedated with medetomidine.

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Medetomidine으로 진정시킨 개에서의 Dexamethaxone의 항구토 효과

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요 약 : Medetomidine으로 마취된 개에 대한 dexamethasone의 항구토 효과를 평가하였다. 실험 당일, medetomidine (40 μg/kg, IM)을 주사하기에 앞서 dexamethasone을 0.25, 0.5, 1.0 mg/kg의 용량으로 정맥주사하였다. 대조군에는 dexamethasone을 대신하여 식염수 0.1 ml/kg를 주사했다. Dexamethasone 0.5, 1.0 mg/kg의 용량에서 구토가 크게 감소되는 것이 관찰되었고, 시각적 마취 점수(visual sedation score)로 측정된 마취의 깊이 정도는 dexamethasone의 전처치에 의해 영향을 받지 않는 것으로 평가되었다. 또한, CBC와 혈액화학분석 수치는 특징적인 변화를 보이지 않았고 실험 전과 하루 후의 수치가 정상범위내에 있었다. 따라서, 본 연구를 통해 medetomidine투여로 유발되는 구토증상을 0.5, 1.0 mg/kg 용량의 dexamethasone이 임상적으로 영향을 끼치지 않으면서 안전하고 효과적으로 예방할 수 있다는 것을 알 수 있었다.

주요어 : Dexamethasone, medetomidine, 항구토 효과, 개.