

## Antiemetic Effect of Dexamethasone in Dogs Sedated with Xylazine

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**Abstract:** This prospective study aimed to assess the efficacy of dexamethasone to prevent xylazine induced emesis in dogs. The antiemetic effect of graded, single high-dose intravenous dexamethasone against xylazine hydrochloride was studied. Clinically healthy mixed breed dogs that weighed  $4.64 \pm 1.25$  kg were used in this study. Food and water were given 3 hours before the experiment. Venous blood specimens were collected from all experimental animals for hematological and blood chemical test pre- and post-experiment. Twenty-eight experimental animals were randomly divided into 4 groups; the group treated with 0.2 ml/kg of normal saline (Control group), the groups treated with 1 mg/kg (D1 group), 2 mg/kg (D2 group) and 4 mg/kg of dexamethasone (D4 group). Three doses of the dexamethasone or normal saline was administered intravenously to each group and after 5 minutes, xylazine (2.2 mg/kg) was administered intramuscularly. The time until onset of the first emetic episode and rate of emesis were investigated. At the same time, the extent of sedation was scored subjectively 5, 15, 30 and 60 minutes after injection of xylazine hydrochloride using Visual Sedation Score. The time until onset of the first emetic episode was  $203.25 \pm 11.35$  sec in Control group,  $187.33 \pm 48.01$  sec in D1 group and  $218.33 \pm 13.58$  sec in D2 group. The rate of xylazine induced emesis were 57% in Control group and 43% in D1 and D2 group respectively. On the other hand, any emetic episodes were not observed in D4 group. At extent of sedation score, all experimental animals especially including the animals in D1 group were highly sedated at 15 minutes after administration of xylazine hydrochloride. Hematological and blood chemical values showed normal ranges pre- and post-experiment. We concluded that prior treatment with 4 mg/kg of dexamethasone hardly caused xylazine-induced emesis without disturbing the sedative effect of xylazine in dogs.

**Key words :** dog, emesis, xylazine hydrochloride, dexamethasone.

### Introduction

Frequently a dog or cat resists restraint, due to either its nature or the procedure to be performed, and thus requires sedation and/or analgesia. Xylazine hydrochloride is a sedative available for use in small animals in the circumstances such as radiography, ultrasonography, catheterization, and skin biopsy<sup>6</sup>. This drug also can be used for oral examination, minor laceration repair, wound debridement, bandage placement, ear canal examination and cleaning, either<sup>14,15</sup>. From clinical experience, the maximum dose of xylazine recommended for sedation of dogs and cats is 1-2.2 mg/kg of intramuscular (IM) injection<sup>6,16</sup>.

While xylazine produces sedation, it has undesirable actions that may be of little consequence if the animal is healthy. These actions include muscle relaxation, anxiolysis, cardiovascular effects, respiratory effects, gastrointestinal effects, renal effects, and hormonal effects<sup>23</sup>. Emesis frequently is reported after administration of xylazine hydrochloride in cats and dogs, which may distress an animal and also increase the risk of aspiration pneumonia<sup>7,12</sup>. Most clinicians would not routinely use prophylactic agents for patients undergoing sedation and would reserve these antiemetics for rescue. Although numerous antiemetics have been studied to prevent or reduce emesis, they have some side effects<sup>5,9,17</sup>.

Among the antiemetics, serotonin subtype-3 (5-HT<sub>3</sub>) antagonists such as tropisetron, ondansetron, granisetron and dro-

peridol are very effective on vomiting, but they are very expensive<sup>8,19</sup>. Other currently used, lower-cost antiemetics include anticholinergics, antihistamines and dopamine receptor antagonists. These drugs have side effects, such as sedation, dry mouth, restlessness, changes in blood pressure, and extrapyramidal symptoms<sup>27,28</sup>. In clinical trials, dexamethasone was shown to be an effective antiemetic drug on Patient Controlled Analgesia (PCA)<sup>5,29</sup>, Postoperative Nausea and Vomiting (PONV)<sup>8,11,21,22,30-33</sup> and cancer chemotherapy<sup>16,20</sup> in humans.

Dexamethasone, a corticosteroid, is a low cost and effective antiemetic drug<sup>16</sup> with minimal side effects after a single-dose administration<sup>16,29</sup>. It was first reported as an effective antiemetic in patients receiving cancer chemotherapy in 1981<sup>12</sup>. Since then, dexamethasone has been widely used to prevent nausea and vomiting. The effective dose of dexamethasone in humans is 8-10 mg in adults<sup>22</sup> and 1-1.5 mg/kg in children<sup>8,16</sup>. Recently, dexamethasone has also been reported to be effective in the prevention of PCA, PONV and chemotherapy in animals<sup>10,18,24,25</sup>. We are not aware of any previous reports about the effect of dexamethasone on nausea and vomiting during sedation with xylazine in dogs. We therefore evaluated the effect of a single dose of dexamethasone on the incidence of vomiting during sedation with xylazine in dogs.

### Materials and Methods

#### Experimental Animals

Twenty-eight adult mixed dogs of either sex that weighed

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4.64±1.25 kg were used in this study. All of them were clinically healthy. They were housed separately in stainless steel cages with room temperature. They were vaccinated with DHPPL (Vanguard Plus 5CV<sup>®</sup>, Pfizer Animal Health Korea Ltd., Korea) and dewormed with febantel (Rintal Tablet<sup>®</sup>, Bayer Health Care Ltd., Korea) 1 month before the experiment. They were fed a commercial dry food (Biomill<sup>®</sup>, Woosung Feed Co Ltd., Korea) and water was always available ad libitum. Twenty-eight experimental animals were randomly divided into 4 groups; the group treated with normal saline and xylazine (Control group), the group treated with 1 mg/kg of dexamethasone and xylazine (D1 group), the group treated with 2 mg/kg of dexamethasone and xylazine (D2 group) and the group treated with 4 mg/kg of dexamethasone and xylazine (D4 group).<sup>2</sup> Seven dogs were allocated to each group. This study was approved by the Kyungpook National University Animal Ethics Committee

### Procedures

All dogs were subjected to the same procedures. Venous blood specimens were collected from all experimental animals for hematology and blood chemistry test pre- and post-experiment: WBC, RBC, PCV, Platelet (PLT), Serum alanine aminotransferase (SALT), Serum aspartate amino-transferase (SAST), Blood urea nitrogen (BUN), creatinine, and Total protein (T-Protein). Food and water were given 3 hours before the experiment.

Before 5 minutes of the induction of sedation, dogs received intravenous (IV) administration of dexamethasone (Dexamethasone disodium phosphate sinil inj<sup>®</sup>, Sinil Pharm Ltd., Korea) at doses of 1, 2 and 4 mg/kg, or 0.2 ml/kg of normal saline. The sedation was induced with xylazine hydrochloride (Rompun<sup>®</sup>, Bayer Health Care Ltd., Korea). The dosage was selected on the basis of effective sedation dose (2.2 mg/kg) and muscles of the caudal thigh group were used as the site for injection. Then dogs were observed for 1 hour to confirm the time until onset of the first emetic episode and frequency of emesis. At the same time, the extent of sedation was scored subjectively 5, 15, 30 and 60 minutes after injection of xylazine hydrochloride. Scoring was done by three observers who were accustomed to assessing sedation score and blinded to the treatments used.

### Assessments

#### 1) Emetic response

Emesis was scored as an all-or-none response as to latency of the first expulsive vomiting. If emesis is occurred, 1 point was added to the group and if emesis is not occurred, no points were added to the group.

Animal behavior was observed for 60 minutes after injection of xylazine and analyzed at the end of the experiment. Emesis was characterized by rhythmic abdominal contractions that were either associated with the oral expulsion of solid or liquid material from the gastrointestinal tract or not associated with the passage of material.

In each animal, the latency to retch or vomit following the administration of the respective emetogen and the number of episodes of retching and/or vomiting were calculated for the duration of the experiment.

#### 2) Total sedation index

Quantification of the extent of sedation was performed using a Visual Sedation Score (VSS). The VSS was modified from the sedation index established by Ansah *et al*.<sup>1,2</sup> (Table 1). The category was divided into posture and gait of experimental animals and degree of resistance to manipulations.

The extent of sedation was scored subjectively 5, 15, 30, and 60 minutes after administration of xylazine. Scores from the above mentioned parameters were summed for each observation time to give total sedation score<sup>3,4</sup>. The maximum possible score at any observation time points was 9. A score of 0 corresponded to a response at the lowest intensity while 9 corresponded to no response even at the highest pinching intensity.

#### 3) Hematology and Blood chemistry test

Blood samples (1.5 ml) were collected from the jugular vein pre- and post-experiment. WBC, RBC, PCV and PLT were evaluated with an auto blood cell analyzer (HEMA VET 850<sup>®</sup>, CDC Technologies Inc., USA) and SALT, SAST, BUN, creatinine and total-protein were measured with an auto dry chemistry analyzer (SPOT CHEM<sup>™</sup> SP-4410<sup>®</sup>,

**Table 1.** Scoring method for sedation in dogs after administration of xylazine hydrochloride

Category	Score
<b>Posture and gait</b>	
Laterally or sternally recumbent, seems asleep, and is not easily wakened by light manipulations.	6
Laterally or sternally recumbent, seems asleep but can be wakened easily by light manipulations.	5
Laterally or sternally recumbent, seems awake but unable to rise or dose not make attempt to rise.	4
Laterally or 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
<b>Degree of resistance to manipulations.</b>	
No resistance to manipulations and no reaction.	3
Moderate resistance to manipulations.	2
Delayed reaction but strong resistance to manipulations.	1
Strong/fairly strong resistance to manipulations.	0
<b>Total sedation index</b>	<b>0-9</b>

Kyoto DAIICHI KANAGU Co. Ltd. Japan).

### Statistical Analysis

All experimental data were expressed as mean±standard deviation. Statistical analysis was performed by DUNCAN test of the one-way ANOVA, with tests for multiple comparisons in SAS program (version 8.1, SAS Institute Inc., Cary, NC). Differences at  $p < 0.05$  were considered statistically significant.

## Results

### Emetic response

#### 1) Latency of xylazine-induced emesis

Most of the emetic episodes occurred during the initial phases of treatment. The time until onset of the first emetic episode in Control group was  $203.25 \pm 11.35$  sec. The time until first emetic episode in D1 and D2 group were  $187.33 \pm 48.01$  and  $218.33 \pm 13.58$  sec respectively. The data had no significant differences among groups (Fig 1).

#### 2) Numbers of episodes of emesis

Numbers of episodes of emesis was 4 heads (57%) in Control group and 3 heads (43%) in D1 and D2 group respectively. No vomiting episodes were observed in D4 group. Converting from these values to percentages, 57% of the dogs developed vomiting in Control group (Fig 2).

### Total sedation index

Total sedation scores were showed in Fig 3. The values of Control group were  $4.10 \pm 2.17$ ,  $4.29 \pm 1.80$ ,  $2.71 \pm 1.70$  and  $0.76 \pm 0.63$  respectively at 5, 15, 30 and 60 minutes after the sedation. The values of D1 group were  $4.29 \pm 2.21$ ,  $5.76 \pm 1.56$ ,  $3.38 \pm 1.74$  and  $1.38 \pm 1.08$  respectively at 5, 15, 30 and 60 minutes after the sedation. The values of D2 group were  $3.81 \pm 0.47$ ,  $3.38 \pm 1.33$ ,  $2.29 \pm 0.72$  and  $1.05 \pm 0.42$  respectively above mentioned times. The values of D4 group were  $4.28 \pm 0.80$ ,  $4.33 \pm 2.06$ ,  $3.43 \pm 2.00$  and  $1.33 \pm 0.92$  respectively above mentioned times. The experimental animals in all groups were sedated highly at 15 minutes after administration of xylazine hydrochloride. Among them, the animals in D1 group obtained the highest sedation score which was significant at 15 min. There were no significant differences for total sedation scores at any dose level except D1 group. These results suggested that any doses of dexamethasone adopted in our study did not affect the degree of sedation.

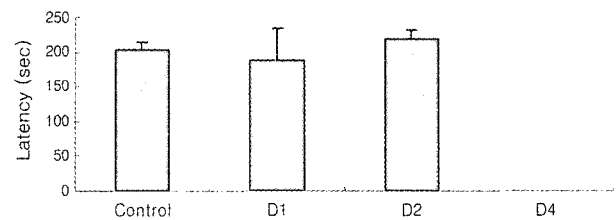
### Hematology and Blood chemistry test

#### 1) Hematology

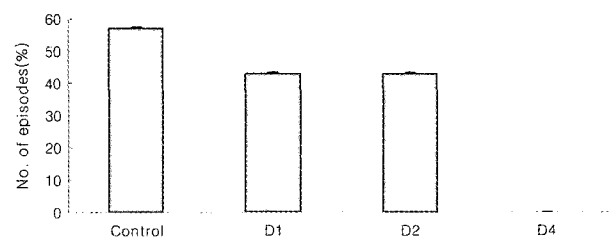
The values of WBC was slightly increased after the experiment, but there were no significant statistical differences among the groups (Table 2).

#### 2) Blood chemistry test

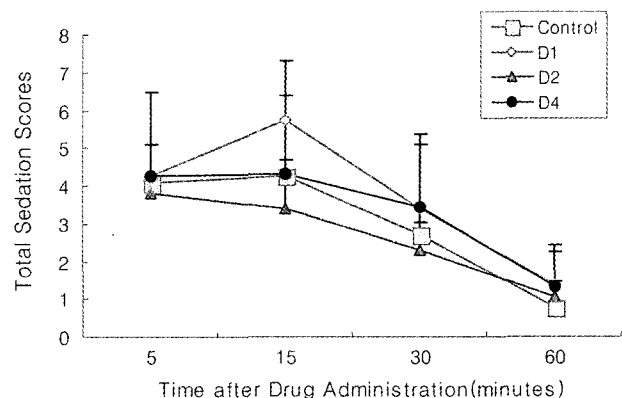
SALT, SAST, BUN, Creatinine and Total-protein values had no significant statistical differences among the groups. The values were remained normally during experiment period



**Fig 1.** The time until onset of first emetic episode in each group. Control: saline solution (2 ml/kg, IV) and xylazine (2.2 mg/kg, IM) D1: dexamethasone (1 mg/kg, IV) and xylazine (2.2 mg/kg, IM) D2: dexamethasone (2 mg/kg, IV) and xylazine (2.2 mg/kg, IM) D4: dexamethasone (4 mg/kg, IV) and xylazine (2.2 mg/kg, IM)



**Fig 2.** Numbers of episodes of emesis in each groups.



**Fig 3.** Total sedation score of 4 groups vs time after xylazine administration.

(Table 3).

## Discussion

Xylazine hydrochloride and medetomidine are two  $\alpha_2$ -agonists approved for use in small animals in the United States<sup>12</sup>. The  $\alpha_2$ -agonists produce good-to-excellent analgesia and moderate-to-profound sedation, and their receptors are located throughout the CNS and are found in great numbers in the superficial laminae of the dorsal horn sensory fibers of the spinal cord and brainstem nuclei<sup>7</sup>.

During the sedation with xylazine hydrochloride, there are several side effects such as bradycardia, decreased myocardial contractility, perfusion and gastrointestinal motility, and depressed thermoregulation<sup>7</sup>. Most of the emetic episodes

**Table 2.** Changes in complete blood count pre- and post-sedation in dogs

		Control	D1	D2	D4
WBC	Pre	9.86±1.17	11.32±0.48	10.74±0.54	20.13±11.50*
WBC	Post	10.3±1.80	20.96±3.20*	17.27±1.51*	23.25±3.78*
RBC	Pre	6.19±0.29	6.10±0.71	6.37±0.35	5.83±0.17
RBC	Post	6.30±0.44	6.25±0.81	6.32±0.09	5.46±0.17
PLT	Pre	407.5±111.90	491.5±92.67	313±87.12	342.5±66.24
PLT	Post	403.5±94.22	513.75±101.2	304.5±116.39	343.5±63.96
PCV	Pre	37.25±2.04	37.85±1.70	36.25±3.04	37.65±0.49
PCV	Post	39.53±1.87	39.90±3.11	37.60±0.71	33.65±2.48

WBC. white blood cell (K/ $\mu$ l)RBC. red blood cell (M/ $\mu$ l),PLT. platelet (K/ $\mu$ l)

PCV. packed cell volume (%)

\* $P < 0.05$ **Table 3.** Changes in serum chemistry values pre- and post-sedation in dogs

		Control	D1	D2	D4
SALT	Pre	61.5±15.39	25.5±16.29*	28±2.82*	38±19.59*
SALT	Post	49.75±13.12	36.5±9.81	34±2.82	51.5±20.50
SAST	Pre	14.5±9	11±1.41	14.5±6.36	10±5.06
SAST	Post	14±8	13.5±4.05	17±5.66	18.5±15.06
BUN	Pre	20.75±10.14	18.75±2.62	13±5.65	27.5±2.12
BUN	Post	15.15±10.01	14.25±4.85	14±2.82	23±2.82
Cre	Pre	0.85±0.31	0.8±0.12	0.85±0.07	0.9±0.56
Cre	Post	0.75±0.24	0.73±0.15	0.8±0.14	0.8±0.28
T-Pro	Pre	7.3±1.17	6.93±0.33	6.85±0.77	6.9±1.06
T-Pro	Post	6.5±0.18	7.55±0.3	7.55±0.07	7.4±1.27

SALT. serum alanine aminotransferase (IU/L)

SAST. serum aspartate aminotransferase (IU/L)

BUN. blood urea nitrogen (mg/dl)

Cre. creatinine (mg/dl)

T-Pro. total protein (g/dl)

\*  $P < 0.05$ 

occurred during the initial phase of treatment<sup>8,13</sup>. Emesis is generally seen within 3-5 minutes after xylazine hydrochloride administration in cats and occasionally in dogs<sup>26</sup>. In considering this point, the latency of emesis was observed for 60 minutes. Xylazine hydrochloride decreases esophageal sphincter pressure in dogs and may increase the likelihood of gastric reflux. In addition, acute abdominal distension has been reported in large-breed dogs after xylazine hydrochloride administration, which may be a result of drug-induced parasympatholytic activity promoting gastrointestinal atony and gas accumulation<sup>23</sup>. Upto 30% of dogs and upto 90% of cats will vomit after xylazine hydrochloride administration, apparently as a result of central stimulation of  $\alpha_2$  adrenoceptors<sup>6</sup>. In this study, 57% of dogs in the Control group and 43% of dogs in the D1 and D2 group vomited respectively. Any dogs did not vomit in D4 group. From the results, it is suggested that the antiemetic

effect of dexamethasone does not act until the dose reaches the optimal limit.

Most clinicians would not routinely use prophylactic agents for patients undergoing sedation and would reserve these antiemetics for rescue. Even if antiemetics are being used to prevent nausea and vomiting, the data are insufficient on which are the most appropriate agents. The controversy about an ideal antiemetic is still existed.

The cost-effectiveness of the various antiemetics is a determination in their use<sup>11</sup>. Recently, dexamethasone has been found to have a prophylactic antiemetic effect on postoperative vomiting in adults and children<sup>8,16</sup>. In addition, in animal studies dexamethasone reduced chemotherapy-induced emesis<sup>9,24,25</sup>. One research reported the combined administration of granisetron and corticosteroids is useful in the inhibition of delayed emesis in ferrets<sup>10</sup>.

The precise mechanism by which dexamethasone, a corticosteroid, exerts an antiemetic action is not fully understood. However, dexamethasone is a potent antiemetic drug that exerts its antiemetic action through the blockage of the corticoreceptors in the nucleus tractus solitarius of the central nervous system<sup>15,16</sup>. That is to say, dexamethasone exerts antiemetic action via prostaglandin antagonism, release of endorphins and tryptophan depletion. And it is known to have an action that reduces the permeability of the blood brain barrier<sup>9</sup>. Dexamethasone may also exert its antiemetic action through some peripheral mechanism<sup>16</sup>.

It was considered dose-response studies were necessary to determine the optimal dose of dexamethasone for the prevention of emesis. In addition, one research suggested that the prophylactic IV administration of dexamethasone immediately before the induction, rather than at the end of anesthesia, was more effective in preventing PONV<sup>32</sup>. Therefore we decided dexamethasone administered 5 minutes before sedation with graded-dose.

Long-term corticosteroid therapy may have significant morbidity such as an increased risk of infection, glucose intolerance, delayed wound healing, superficial ulceration of gastric mucosa, and adrenal suppression<sup>23</sup>. However, side-effects from brief(24-48 h), even high-dose, corticosteroid treatment have been rare<sup>30</sup>.

Larger doses of dexamethasone may have more antiemetic efficacy but are likely to be unacceptably sedating. To confirm the existence of this action, VSS was performed. The experimental animals in all groups were sedated effectively at 15 minutes after administration of xylazine hydrochloride. Except that D1 group at 15 minutes, there were no significances for total sedation scores at any dose level groups. These results suggested that any doses of dexamethasone adopted in our study did not affect the degree of sedation. In our studies, prophylactic treatment in D4 group significantly decreased xylazine-induced emesis without disturbing the sedative effects of xylazine in dogs. These results match those of studies with cats sedated with xylazine<sup>18</sup>. One different thing is dexamethasone is not related to the time until onset of the first emetic episode after xylazine injection. And there are few reasons to pay attention to the adverse effects about the usage of dexamethasone. There is little doubt that dexamethasone is an effective intravenous antiemetic for use in the pre-sedative period in a single intravenous bolus. Considering high dose usage of dexamethasone or high cost of 5-HT<sub>3</sub> receptor antagonists, the use of proper antiemetic drugs is required. Therefore, it is imperative that more studies are required to be carried out in this area, particularly in evaluating the efficacy of corticosteroids, 5-HT<sub>3</sub> receptor antagonists, or a combination of both. The 5-HT<sub>3</sub> antagonists also were used effectively combined with dexamethasone in humans<sup>16</sup>. When prophylaxis with dexamethasone fails to prevent PONV, the combination with a small-dose 5-HT<sub>3</sub> receptor antagonist has been recommended<sup>11</sup>. Double and triple antiemetic combinations are recommended for patients at high risk for PONV<sup>11</sup>.

In our study, it was not considered any risk factors such as age, sex and breed that could modify the incidence of vomiting as background among the groups. In spite of the acknowledged limitations of this study, our study provided valuable information concerning the high prevalence of vomiting, especially that associated with xylazine, that is important to today's practitioners.

As shown in this study, dexamethasone is more useful as antiemetics in terms of efficacy compared with placebo. Further studies are required about the precise mechanisms and more effective methods of dexamethasone.

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## Xylazine hydrochloride로 진정시킨 개에 대한 Dexamethasone의 항구토 효과

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**요약** : Xylazine hydrochloride로 진정한 개에서 발생하는 구토에 대한 dexamethasone의 항구토 효과를 평가하고자 본 실험을 수행하였다. 4.64±1.25 kg의 임상적으로 건강한 28마리 잡종견을 사용하였으며, 사료공급과 음수공급은 실험 3시간 전 실시하였다. 실험 전과 후 정맥에서 채혈하여 혈액검사와 혈청화학검사를 실시하였다. Dexamethasone 1 mg/kg (D1군), 2 mg/kg (D2군), 4 mg/kg (D4군) 또는 생리 식염수 0.2 ml/kg (Control군)를 정맥내 주사하고 5분 후에 xylazine hydrochloride를 근육내 주사하여 진정시켰다. 각각 구토 발생시간과 구토 유무를 측정하였고, xylazine hydrochloride 진정 후 5, 15, 30, 60분에 Visual Sedation Score를 사용하여 진정정도를 평가하였다. 구토 발생시간은 대조군에서 203.25±11.35초였고, D1군과 D2군에서 각각 187.33±48.01초와 218.33±13.58초로 차이가 없었다. 구토율은 D4군 전체 실험견이 구토를 보이지 않는 반면, Control군 실험견 중 57%가 구토를 하였고, D1군과 D2군 실험견들은 각각 43% 구토율을 나타냈다. 진정 정도는 실험군에 관계없이 dexamethasone을 투여한지 15분 후에 높은 수치를 나타냈다. 혈액검사, 혈청화학검사결과는 정상수치를 보였다. 이상 결과로, 개에서 진정치로 사용한 4 mg/kg 용량 dexamethasone은 진정작용에 관계없이 xylazine hydrochloride가 유발시키는 구토를 예방한다는 것을 알 수 있다.

**주요어** : xylazine, 구토, 개, dexamethasone.