Antiemetic efficacy of promethazine on xylazine-induced emesis in cats

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Abstract — The prophylactic antiemetic effect of 3 dosages of promethazine injected into cats 1 h before administration of xylazine was compared with that of a saline solution. Prior treatment with 2 and 4 mg/kg of promethazine significantly reduced the frequency of emetic episodes. Promethazine may be used as a prophylactic antiemetic in cats treated with xylazine.

Résumé — Efficacité anti-émétique de la prométhazine sur les vomissements induits par la xylazine chez les chats. L'effet anti-émétique prophylactique de 3 doses de prométhazine injectées chez les chats 1 heure avant l'administration de la xylazine a été comparé avec celui d'une solution saline. Un traitement préalable avec 2 et 4 mg/kg de prométhazine a significativement réduit la fréquence d'épisodes émétiques. La prométhazine peut être utilisée comme un anti-émétique prophylactique chez les chats traités avec de la xylazine.

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Xylazine hydrochloride, an α2-adrenoceptor agonist, possessing analgesic, sedative, and muscle relaxant properties, has been widely used in veterinary practice following its introduction in 1962 (1). Xylazine frequently induces emesis in cats, thereby running the risk of aspiration pneumonia (2). This effect is mediated by α2-adrenoreceptors placed in the chemoreceptor trigger zone (CTZ) of the area postrema in cats (3). Alpha2-adrenoreceptor antagonists such as yohimbine, tolazoline, or phentolamine inhibit xylazine-induced emesis in cats but also prevent its sedative effects (4). The area postrema is very rich in biogenic amines, including histamine which stimulates the medullary CTZ, producing nausea and vomiting (5). Promethazine is a first-generation H1 receptor antagonist of the phenothiazine chemical class that competitively blocks histamine H1 receptors without blocking the secretion of histamine. It is also a very weak dopamine antagonist (6). Promethazine appears to have an antiemetic effect due to its antagonism of central histamine receptors. Since α2-adrenoreceptors, histamine, and dopamine receptors exist in the CTZ of the area postrema in cats, we hypothesized that prophylactic administration of promethazine may prevent vomiting in cats treated with xylazine HCl.

Eight healthy adult cats (4 of each gender) weighing between 1.4 and 2.8 kg (median, 2 kg) were vaccinated with feline rhinotracheitis-calici-panleukopenia vaccine (Fort Dodge Animal Health, Fort Dodge, Iowa, USA) and a rabies vaccine (Rabisin-R; Mérial, Lyon, France), prior to the study. The cats were housed separately in single cages placed in a well-ventilated room with temperature controlled at 22 ± 2°C and were fed a commercial cat food. Water was available *ad libitum.* The protocol for the study was approved by the institutional animal care committee, Faculty of Veterinary Medicine, University of Tabriz, Iran.

The prophylactic antiemetic effect of 3 doses of promethazine HCl [1, 2, and 4 mg/kg body weight (BW), IM] (Promethazine; Tehran Chemie, Tehran, Iran), selected on the basis of a preliminary study, was evaluated against saline (0.9% NaCl) solution (0.1 mL/kg BW, IM) as a control treatment. Control and drug treatments were injected 1 h before administration of xylazine (0.66 mg/kg BW, IM) (Xylazine, 2%; Alfasan, Woerden, The Netherlands). Saline was administered to the cats on day 0, and promethazine at 1, 2, and 4 mg/kg was administered on days 7, 14, and 21, respectively. All the cats were subjected to the same procedures, and food was withheld on the night preceding each treatment. Promethazine was diluted in saline solution to achieve an injection volume of 0.2 mL. Immediately after each injection of promethazine, the cats were provided with 150 g of commercial cat food. One hour later, xylazine was administered to each cat (0.66 mg/kg, BW, IM). A 2% solution of xylazine was diluted with saline solution to achieve the final injection volume of 0.2 mL.

Emesis was scored as an all-or-none response, and separate episodes of emesis were recorded when the interval between bouts of vomiting exceeded 5 s. During a 30-minute observation period after injection of xylazine, the time to onset of emesis and the number of episodes of emesis were noted. Productive emesis (food or bile) was recorded in this study and retching was excluded from the study. A sedative response was recorded when

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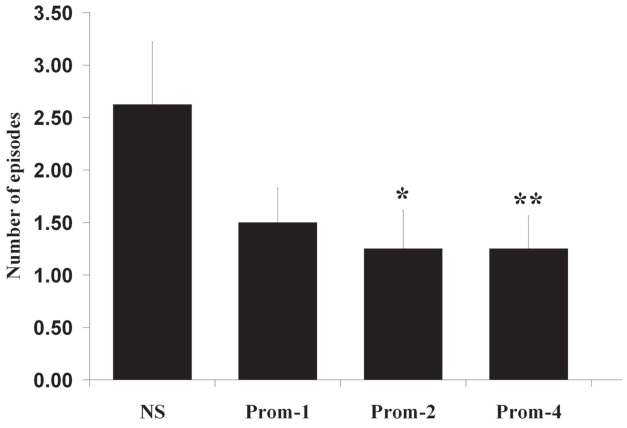

Figure 1. Effect of 3 doses of promethazine (Prom-1, 1 mg/kg BW; Prom-2, 2 mg/kg BW; and Prom-4, 4 mg/kg BW) compared with normal saline (NS) on the number of episodes of emesis in 8 healthy adult cats sedated with xylazine hydrochloride (0.66 mg/kg BW, IM). Results are presented as means ± standard error of the mean. *$P = 0.036$, **$P = 0.008$, compared with control treatment (normal saline).

a cat assumed sternal or lateral recumbency and was unable to stand on its own. Time until onset of sedation after administration of xylazine was recorded.

All data were reported as mean ± standard error of the mean (S_x). Data for the time until onset of sedation, latency of emesis, and frequency of emesis after treatment with promethazine were analyzed, using the Wilcoxon signed-rank test. A two-sided test was used and a value of $P < 0.05$ was considered significant.

Treatment with promethazine at 1, 2, and 4 mg/kg did not significantly alter the time until onset of the first emetic episode in cats sedated with xylazine hydrochloride. Time until onset of the first emetic episode (mean ± S_x) was 4.17 ± 0.48 min when cats were administered the control saline solution prior to administration of xylazine. When cats were administered doses of 1, 2, or 4 mg of promethazine/kg BW prior to administration of xylazine, times until first emetic episode were 4.86 ± 0.77, 5.17 ± 0.60, and 3.86 ± 0.51 min, respectively.

Number of episodes of emesis was 2.63 ± 0.60 for the saline treatment, and 1.50 ± 0.33, 1.25 ± 0.37, and 1.25 ± 0.31 for promethazine at dosages of 1, 2, and 4 mg/kg BW, respectively. Prior treatment with promethazine at dosages of 2 and 4 mg/kg BW significantly reduced the number of episodes of emesis induced by xylazine (Figure 1). Time until onset of sedation was 12.25 ± 1.45 min for the saline treatment and 11.33 ± 2.17, 14.38 ± 1.53, and 10.57 ± 1.74 minutes for promethazine at dosages of 1, 2, and 4 mg/kg BW, respectively. Prior treatment with promethazine did not significantly alter time to onset of sedation after administration of xylazine.

This study showed that prior intramuscular treatment with 2 and 4 mg/kg of promethazine significantly reduced the frequency of emesis with no significant effect on the time to the first emetic episode after xylazine injection. Phenothiazine agents such as promethazine have been widely used as antiemetics in patients with morning sickness (7), motion sickness (8), or following surgery (post-operative nausea and vomiting) (9). The prominent mechanism of action is antagonism of central histamine and dopamine receptors (6) but the effect of promethazine on xylazine-induced emesis in cats has not been studied previously. We have shown that metoclopramide significantly reduces the frequency of emetic episodes induced by xylazine with no effect on the time until onset of the first emetic episode (10). Others have shown that prior treatment with dexamethasone prevents xylazine-induced emesis in cats through activation of the glucocorticoid receptors in the bilateral nucleus tractus solitarii (NTS) in the medulla oblongata (11). In this respect, maropitant, a potent neurokinin 1 receptor antagonist, reduced the mean number of emetic events induced by xylazine in cats. Maropitant has a low affinity for adrenergic receptors including the α2-adrenergic receptor (12).

In line with these findings, the present study showed that prior treatment with promethazine is effective in reducing the frequency of xylazine-induced emesis in cats, but the mechanisms involved in this effect are not clear. It is well-known that the medulla oblongata has substantial neuronal activity in regulation of the emetic reflex (13) and NTS is richly supplied with many kinds of vomiting-related neurotransmitters and neuromodulators, such as opioid, gamma-amino butyric acid (GABA), adrenaline, noradrenaline, dopamine, serotonin, histamine, and substance P (14). Also, some authors have hypothesized that the bilateral NTS may be the common final pathway that leads to the vomiting center (15). It is assumed that promethazine, a histamine and dopamine receptor antagonist (like metoclopramide, dexamethasone, and maropitant), doesn't inhibit α2-adrenoreceptors for its antiemetic action and produces its antiemetic action on xylazine-induced emesis via inhibiting histamine and dopamine receptors in the bilateral NTS in this nervous pathway. The mechanism of this effect remains to be studied in detail; however, our results showed that promethazine in any of the dosages did not alter the time to onset of sedation of cats injected with xylazine HCl.

In conclusion, the present study indicates that promethazine (2 and 4 mg/kg, IM) significantly reduces the frequency of emetic episodes induced by xylazine with no effect on the time until onset of the first emetic episode. Promethazine may be used as a prophylactic antiemetic in cats treated with xylazine HCl. CVJ

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Answers to Quiz Corner
Les réponses du test éclair

1. **d)** Female hamsters should be housed alone after breeding because they may attack and kill the male. They should not be disturbed for at least 1 week following parturition, because any disturbance could cause them to cannibalize their young. In all other species listed, the male helps care for the young.

d) Les femelles hamsters doivent être placées seules dans une cage après l'accouplement, parce qu'elles peuvent attaquer et tuer les mâles. Elles ne doivent pas être dérangées durant au moins une semaine après la parturition, parce que toute perturbation peut causer du cannibalisme envers les jeunes. Chez toutes les autres espèces, le mâle contribue aux soins des petits.

2. **b)** Cholinesterase activity is most concentrated in red blood cells.

b) L'activité cholinestérasique est plus concentrée dans les globules rouges.

3. **e)** Endoscopy is not as good as fluoroscopy in demonstrating esophageal function. Metoclopramide does not improve esophageal function. Although some affected animals can be managed well with dietary therapy, the prognosis is guarded, since many die from aspiration pneumonia. Cisapride appears to be of benefit in rare cases, possibly in dogs with gastroesophageal reflux.

e) L'endoscopie n'est pas aussi efficace que la fluoroscopie pour démontrer la fonction œsophagienne. Le métoclopramide n'améliore pas la fonction œsophagienne. Bien que certains animaux atteints puissent être bien traités à l'aide d'un traitement diététique, le pronostic est réservé puisque plusieurs meurent de pneumonie par aspiration. Le cisapride semble être bénéfique dans de rares cas, possiblement chez les chiens manifestant du reflux gastro-œsophagien.

4. **d)** Stress-associated hyperglycemia is not an appropriate differential diagnosis for syncope or intermittent weakness.

d) L'hyperglycémie associée au stress n'est pas un diagnostic différentiel approprié pour la syncope ou la faiblesse intermittente.

5. **b)** Thiacetarsamide must be given by careful intravenous injection because perivascular injection causes severe tissue irritation and sloughing.

b) La thiacétarsamide doit être administrée par injection intraveineuse minutieuse parce que l'injection périvasculaire cause de l'irritation tissulaire et des escarres.

6. **d)** Culture and sensitivity tests are the best way to determine which antibiotic is appropriate for treatment.

d) La culture bactérienne et l'antibiogramme sont la meilleure façon de déterminer quelle antibiothérapie est appropriée.

7. **c)** Perineal urethrotomy is typically performed for temporary urinary diversion in males with obstructive urinary outflow disease.

c) L'urétrotomie périnéale est réalisée de façon caractéristique pour la dérivation urinaire temporaire chez les mâles qui souffrent d'écoulement urinaire obstructif.

8. **a)** Colic is the most common clinical sign associated with uterine torsion in mares.

a) Les coliques sont le signe clinique le plus fréquent associé à la torsion utérine chez la jument.

9. **b)** Caudal paresis after calving is usually associated with damage to the sciatic nerve.

b) La parésie caudale à la suite du vêlage est habituellement associée à l'atteinte du nerf sciatique.

10. **d)** Septicemia in neonatal calves is most frequently associated with *E. coli*.

d) La septicémie chez le veau nouveau-né est plus couramment associée à *Escherichia coli*.