

## Effects of Ondansetron on Xylazine Induced Emesis in Cats

Seyedhosein Jarolmasjed<sup>\*1</sup>, DVM, DVSc  
Saeed Kolahian<sup>2</sup>, DVM, PhD

<sup>1</sup> Department of Clinical Sciences, Faculty of Veterinary Medicine,  
University of Tabriz, Iran

<sup>2</sup> Department of Basic Sciences, Faculty of Veterinary Medicine,  
University of Tabriz, Iran

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### Abstract

**Objective-** Vomiting frequently is reported after xylazine administration in cats. This study evaluates prophylactic antiemetic efficacy of ondansetron in cats sedated with xylazine HCl.

**Design-** Experimental study.

**Animals-** Six healthy adult cats from both genders were selected for the study.

**Interventions-** Intramuscular injection of normal saline was administered an hour before intramuscular injection of xylazine (0.66 mg/kg) on day 0 (control treatment). Ondansetron was injected in three increasing dosages (0.2, 0.4 and 0.8 mg/kg) an hour prior to administration of xylazine on days 7, 14 and 21, respectively (experimental treatments). All the cats were fed with commercial food after ondansetron or saline injection.

**Measurements and Main Results-** They were monitored after injection of xylazine for thirty minutes to record the onset of first emetic response, frequency of emetic episodes and the onset of recumbency. All data were analyzed using Wilcoxon signed-rank test. Prior treatment with each dosage of ondansetron significantly reduced the frequency of emetic episodes ( $p < 0.05$ ). Ondansetron administration prior to xylazine injection didn't increase the time until onset of the first emetic episode and also onset of recumbency at any of mentioned dosages.

**Conclusions and Clinical Relevance-** Ondansetron may be used as a prophylactic antiemetic in cats sedated with xylazine HCl.

**Key words-** Cats, ondansetron, sedation, vomiting, xylazine

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### \* Corresponding author:

Seyedhosein Jarolmasjed, DVM, DVSc

Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Tabriz,

Tabriz, Iran. Postal Code: 5166616471

Tel: +98 (411) 3392342 Fax: (+98) 411 3357834

E-mail: Jarolmasjed@tabrizu.ac.ir

## Introduction

Xylazine [Rompun; BAY 1470; 2-(2,6-dimethylphenylamino)-4H-5,6-dihydro-1,3-thiazine] is an alpha2-agonist with sedative, analgesic and muscle relaxant properties that is commonly used in small animals anesthesia to perform procedures such as radiography, ultrasonography, catheterization, and biopsy.<sup>1</sup> However, vomiting frequently is reported after xylazine administration in cats<sup>2-7</sup> and dogs,<sup>8,9</sup> which may distress an animal and also increase the risk of pulmonary aspiration of gastric content.<sup>10</sup> Antagonists of alpha2-adrenoceptors can control xylazine induced emesis, but they also antagonize the sedative effects of xylazine.<sup>5,6,9,11,12</sup>

At present, 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonists are primarily used to control chemotherapy- and radiotherapy-induced nausea and vomiting (CINV) and in postoperative nausea and vomiting (PONV).<sup>13</sup> There is also clinical evidence that 5-HT<sub>3</sub> receptor antagonists could be useful for the alleviation of vomiting during pregnancy and following caesarean section.<sup>14,15</sup> Ondansetron has high binding affinity for the 5-HT<sub>3</sub> receptor.

This study was conducted to evaluate prophylactic antiemetic efficacy of ondansetron in cats sedated with xylazine HCl. The effect of this premedication was also investigated on the time until onset of sedation in cats treated with xylazine HCl.

## Materials and Methods

Six healthy adult domestic short hair cats (3 of each gender) weighing between 2.3 and 3.5 kg (median, 2.75 kg) were used in the study. Cats were housed separately in single cages placed in an air-ventilated room with temperature controlled at 22±2°C. They were fed a commercially available food, and water was available ad libitum. The protocol for the study was approved by institutional animal care and use committee.

### *Procedure*

The antiemetic efficacy of three dosages of ondansetron (Demitron 2 mg/ml, Tehran Chemie pharmaceutical co., Iran, intramuscular injection (IM)) an hour before administration of xylazine HCl (Alfasan, 2%, the Netherlands, IM) was evaluated against saline solution (0.9% NaCl) as a placebo. All cats were subjected to the same procedures, and each treatment was conducted at one-week intervals. They were initially administered with intramuscular injection of normal saline (0.074 ml/kg of body weight) on day 0 (control treatment). Ondansetron was injected in three increasing dosages (0.2, 0.4 and 0.8 mg/kg) on days 7, 14 and 21, respectively. Immediately after injection of saline solution or ondansetron, cats were fed with 150g of commercial food. An hour later, the dose of 0.66 mg/kg of xylazine HCl diluted in sterile normal saline to reach an injection volume of 0.2 ml was administered intramuscularly. Injection of the selected dose of xylazine is effective to induce emesis in 95% of cats.<sup>2,3</sup> All the cats were observed for thirty minutes after xylazine injection to record the time needed for onset of first emetic response, frequency of emetic episodes and the time of onset of recumbency,.

### *Emetic and sedative responses*

Emesis was scored as an all-or-none response, and separate episodes of emesis were considered when the interval between bouts of vomiting exceeded 5 seconds. The time from xylazine injection to the onset of the first emetic episode was recorded in minutes. During 30-

minute observation period, the number of episodes of emesis was also counted. Premonitory signs of emesis such as salivation and licking were not considered an emetic response. Sedative response was recorded when a cat assumed sternal or lateral recumbency and was unable to stand. The time until onset of sedation after administration of xylazine was also recorded.

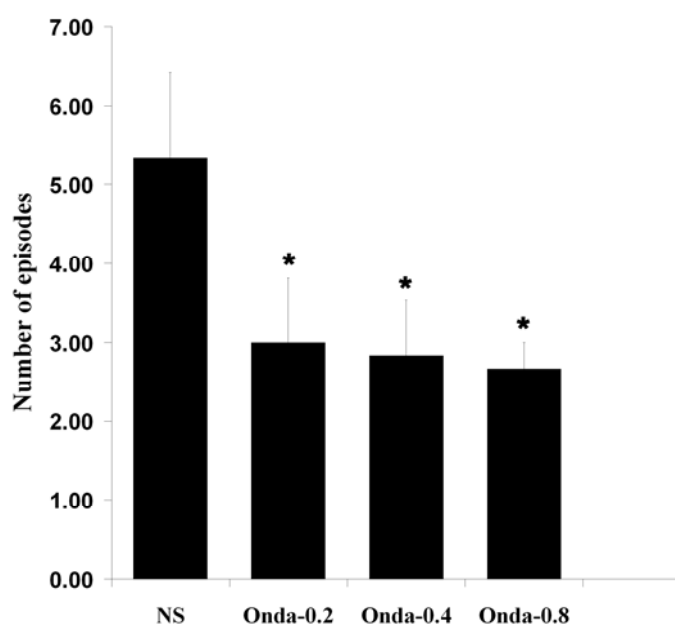
### Statistical analysis

All data were reported as mean  $\pm$  SEM. Data for the time until onset of first emetic episode, frequency of emetic episodes and the time needed for onset of recumbency after treatment with ondansetron were analyzed using the Wilcoxon signed-rank test. Statistical testing was performed using Sigma Stat 2.03 for Windows (SPSS, Inc., Chicago, IL); *p* values less than 0.05 were considered significant.

### Results

All cats pretreated with saline solution (control treatment) showed episodes of emesis after receiving 0.66 mg/kg of xylazine HCl and vomited most of the food they were fed (mean $\pm$ SEM) (number of episodes of emesis was 5.33 $\pm$ 1.09). Number of episodes of emesis was 3.00 $\pm$ 0.82, 2.83 $\pm$ 0.70 and 2.67 $\pm$ 0.33 for ondansetron at dosages of 0.2, 0.4 and 0.8 mg/kg, respectively. Pretreatment of cats with ondansetron at any mentioned dosages significantly reduced the number of episodes of emesis induced by xylazine HCl (Fig. 1). This effect was not dose dependant.

The time until onset of the first emetic episode and the time until onset of sedation after administration of saline solution or 0.2, 0.4 and 0.8 mg/kg of ondansetron prior to administration of xylazine were shown in Table 1. Pretreatment of cats with mentioned dosages of ondansetron could not significantly increase the time until first emetic episode after administration of xylazine HCl. Prior treatment with ondansetron at any of these dosages did not significantly alter the time until onset of sedation after administration of xylazine.



**Figure 1-** Effect of IM administration of three different dosages of ondansetron compared to normal saline (NS) an hour before IM administration of xylazine on the number (mean $\pm$ SEM) of episodes of xylazine-induced emesis in 6 cats. Treatments were as follows: control treatment (NS), 0.074 ml/kg; Onda-0.2, 0.2 mg/kg; Onda-0.4, 0.4 mg/kg; and Onda-0.8, 0.8 mg/kg. Values that differ significantly (*P* < 0.05) from the value for the control treatment are indicated with\*.

**Table 1-** Effects of administration of saline solution or different dosages of ondansetron prior to administration of xylazine (0.66 mg/kg) on the latency time of emesis and time until onset of sedation. Data represent mean±SEM of 6 animals for each experiment.

Treatments	Dosages	Latency time of emesis (min)	Time until onset of sedation (min)
Normal Saline	0.074 ml/kg	4.60 ± 0.24	15.20 ± 2.31
Ondansetron	0.2 mg/kg	3.67 ± 0.49	13.00 ± 2.30
Ondansetron	0.4 mg/kg	4.00 ± 0.45	12.20 ± 1.20
Ondansetron	0.8 mg/kg	3.50 ± 0.22	13.40 ± 1.72

## Discussion

This study was conducted to evaluate prophylactic antiemetic efficacy of ondansetron in sedated cats with xylazine HCl. In this study, we found that prior administration of ondansetron (0.2, 0.4 and 0.8 mg/kg, IM) has significantly reduced frequency of emetic episodes in xylazine injected cats. However, mentioned dosages could not significantly increase the time until onset of emesis and also there was no significant difference on the onset of recumbency between control and treatment groups after injection of xylazine. Therefore, ondansetron could be valuable for prophylactic use as an antiemetic in cats sedated with xylazine.

Due to its antiemetic properties, ondansetron has been used to treat nausea and vomiting after chemotherapy.<sup>16</sup> The 5-HT<sub>3</sub> receptor antagonists have been regarded as the ‘gold standard’ in antiemetic therapy. Numerous studies investigating the use of ondansetron and granisetron have shown that when delivered intravenously both drugs are safe and highly effective in preventing nausea and vomiting induced by moderately high or highly emetogenic chemotherapy in humans.<sup>17-19</sup>

It is shown that ablation of area postrema of the medulla oblongata in cats results in elimination of the emesis induced by xylazine, but it doesn't affect the general sedative effect of the standard dose (0.66 mg/kg) of the medicine. Thus xylazine acts on the chemoreceptor trigger zone (CTZ) of the area aostrema to induce emesis.<sup>3</sup>

Numerous studies have tested different antiemetic drugs in preventing xylazine induced vomiting. In this respect, it has been shown that prior treatment with dexamethasone effectively prevents xylazine induced emesis in cats.<sup>1,20</sup> There are large amount of glucocorticoid receptors and alpha 2-adrenoceptors together in the area postrema and nucleus of the solitary tract in the medulla oblongata.<sup>21,22</sup> Medulla oblongata, having substantial neuronal activity, is responsible for controlling reflex centers of vomiting.<sup>23</sup> It has been shown that dexamethasone exerts its central antiemetic action in decerebrated cats sedated with xylazine, via activation of the glucocorticoid receptors in the bilateral nucleus tractus solitarii (NTS) of the medulla.<sup>24</sup> In this respect, maropitant, a potent neurokinin 1 receptor antagonist reduced the mean number of emetic events induced by xylazine. It is reported that maropitant has a low affinity at adrenergic receptors including the alpha2 adrenergic receptor.<sup>25</sup> Maropitant acts highly selective for the neurokinin 1 receptor and did not prevent xylazine induced emesis via antagonizing the alpha 2-adrenoceptors.<sup>25</sup> Promethazine has also been investigated in cats as antiemetic decreasing episodes of xylazine induced emesis.<sup>26</sup> Furthermore, the antiemetic efficacy of metoclopramide has been shown in cats sedated with xylazine. It has been suggested that metoclopramide, a dopamine and serotonin receptor

antagonist, like dexamethasone, maropitant and promethazine doesn't inhibit alpha 2-adrenoceptors for its antiemetic action and accomplishes the antiemetic action on xylazine induced emesis through inhibition of dopamine and serotonin (5-HT<sub>3</sub>) receptors in the bilateral NTS of medulla oblongata in this nervous pathway.<sup>27</sup> 5-HT<sub>3</sub> receptors are located in many brain areas including the hippocampus, entorhinal cortex, frontal cortex, cingulate cortex, amygdala, nucleus accumbens, substantia nigra and ventral tegmental area, with highest levels in the brain stem, especially areas involved in the vomiting reflex such as the area postrema and the NTS. These brain regions are protected by the blood–brain barrier with the exception of the area postrema and the nucleus tractus solitarius. 5-HT<sub>3</sub> receptors have also been detected in the dorsal horn and dorsal root ganglia of the spine and in combination with the area postrema are responsible for the vomiting reflex.<sup>13</sup> Since coordination of vomiting is accomplished by the same region of CNS without any dependence to causing stimulus, it sounds that precise targeting of the key neurotransmitter receptors in the NTS can control vomiting.<sup>28</sup>

Using radioligand-binding techniques to measure the affinity of ondansetron has been demonstrated that ondansetron exhibits high binding affinity for 5-HT<sub>3</sub> receptors. Ondansetron also has detectable binding at 5-HT<sub>1B</sub>, 5-HT<sub>1C</sub>, alpha 1-adrenergic, and opioid  $\mu$  sites.<sup>29</sup> This fact may also contribute to conclusion that, 5-HT<sub>3</sub> receptors are found pre- and postsynaptically and activation can modulate the release of a variety of neurotransmitters, including dopamine, cholecystokinin, GABA, substance P and acetylcholine.<sup>13</sup>

In this regard, we hypothesize that ondansetron may not inhibit alpha 2-adrenoceptors for its antiemetic action; rather it may exert its antiemetic action on xylazine induced emesis indirectly on vomiting center in medulla oblongata and block vomiting pathways via antagonizing 5-HT<sub>3</sub> receptors of the area postrema. Further investigation is needed to study the exact antiemetic mechanism of ondansetron on xylazine induced emesis in cats.

In conclusion, the results of this study showed that pretreatment with ondansetron at dosages of 0.2, 0.4 and 0.8 mg/kg in cats significantly reduces the frequency of emetic episodes induced by xylazine with no significant increase in the time until onset of the first emetic episode and the time until onset of sedation following administration of xylazine.

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## اثرات اندانسترون بر استفراغ ناشی از زایلازین در گربه ها

سیدحسین جارالمسجد<sup>۱</sup>، سعید کلاهیان<sup>۲</sup>

<sup>۱</sup> گروه علوم درمانگاهی پایه دانشکده دامپزشکی، دانشگاه تبریز، تبریز، ایران  
<sup>۲</sup> گروه علوم پایه دانشکده دامپزشکی، دانشگاه تبریز، تبریز، ایران.

**هدف-** به دنبال تجویز زایلازین در گربه اغلب استفراغ رخ می دهد، این مطالعه اثرات ضد استفراغی اندانسترون را در گربه هایی که با زایلازین آرام شده اند ارزیابی می نماید.

**طرح-** مطالعه تجربی

**حیوانات-** شش گربه بالغ سالم از هر دو جنس نر و ماده

**روش کار-** در روز صفر، سالین نرمال یک ساعت قبل از تزریق زایلازین (۰/۶۶ میلی گرم بر کیلوگرم) به صورت داخل عضلانی به تمامی حیوانات تزریق گردید (کنترل). سپس در روزهای هفت، چهارده و بیست و یک، اندانسترون به ترتیب در سه دوز ۰/۲، ۰/۴ و ۰/۸ میلی گرم بر کیلوگرم یک ساعت قبل از تجویز زایلازین به حیوانات تزریق گردید. به دنبال تجویز اندانسترون یا سالین نرمال به تمامی گربه ها اجازه غذا خوردن داده شد. پس از تزریق زایلازین، تمامی گربه ها به مدت نیم ساعت تحت نظر قرار گرفتند تا پارامترهایی نظیر زمان اولین استفراغ، تعداد استفراغ و زمان مشاهده اثر آرام بخشی زایلازین ثبت گردند.

**نتایج-** درمان پیش گیرانه با هر یک از دوز های اندانسترون باعث کاهش معنی داری در تعداد دفعات استفراغ گردید. این دارو نتوانست تاثیر معنی داری بر زمان مشاهده اولین استفراغ داشته باشد. همچنین هیچ یک از دوز های مورد استفاده، تاثیری بر مدت زمان القای آرام بخشی زایلازین نداشتند.

**نتیجه گیری-** بنابراین می توان اظهار کرد که اندانسترون می تواند بدون تاثیر بر زمان آرام بخشی، به عنوان داروی پیش گیری کننده از استفراغ در گربه هایی که با زایلازین تسکین یافته اند عمل نماید.

کلید واژگان: گربه، اندانسترون، آرام بخشی، استفراغ، زایلازین.