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Efficacy of Different Antiemetics with Different Mechanism of Action on Xylazine Induced Emesis in Cats

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Abstract

Xylazine hydrochloride, α2 adrenoceptor agonist, is an analgesic, sedative, tranquilizer, and muscle relaxant agent in veterinary medicine which is mostly used as in pre-anesthesia in veterinary medicine. One of the main adverse effects of xylazine which limits application of this medication in small animal veterinary practice (mostly in cats) is nausea and vomiting which can end up with aspiration pneumonia. In this review, we will discuss the efficacy of prophylactic administration of different antiemetics with different mechanism of action in preventing vomiting in cats treated with xylazine hydrochloride. All medications such as acepromazine, promethazine, metoclopramide, ondansetron, dexamethasone, maropitant and vitamine B6 have been shown to have antiemetic efficacy on xylazine induced emesis in cats. These mentioned medications have different antiemetic mechanism of actions. It can be concluded that all these medications not only inhibit α2 adrenoceptor but also may exert their antiemetic effects directly on nucleus tractus solitarius and vomiting center.
Keywords: Emesis, Cat, Xylazine, Antiemetic

Introduction

Xylazine hydrochloride is an analgesic, sedative, tranquilizer, and muscle relaxant agent in veterinary medicine.[1] Xylazine-induced emesis, mediated by α_2 adrenoceptor placed in chemoreceptor trigger zone (CTZ) of the area postrema, occurs frequently in cats, and hence increases the risk of aspiration pneumonia.[2-4] Using an α_2 adrenoceptor antagonist such as yohimbine, tolazoline, and phentolamine inhibits xylazine-induced emesis in cats but also prevents its sedative effects in these animals.[5-7] On the other hand, it is well-known that the medulla oblongata has substantial neuronal activity in regulation of the emetic reflex[8] and nucleus tractus solitarius (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.[9, 10] In this review, we will discuss these recent findings on the efficacy of prophylactic administration of different antiemetics which are acting via different mechanisms (including neurotransmitters and receptors), in preventing vomiting in cats treated with xylazine hydrochloride.

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Introduction of Xylazine

Xylazine hydrochloride was synthesized in Germany in 1962 and was the first α_2 adrenergic agonist to be used as sedative, tranquilizer, analgesic and muscle relaxant by veterinarian.[1] The sedative effect is because of central α_2 adrenergic agonist action.[11] Enhancement of the analgesic response may also occur as the result synergistic interaction between α_2 adrenergic agonist and opiates in the spinal cord.[12] It has more, better and longer visceral analgesic effect than butorphanol, meperidine and penthazocine.[13] Xylazine relaxes muscles by inhibition of interneuronal transmission of impulses at the central level of the CNS.[14] All these beneficial effects of xylazine make this medication significantly more valuable than other sedatives and tranquilizers like benzodiazepines and phenothiazines for veterinary use. One of the main side effect of xylazine in small animal practice (especially in cats and less important in dogs) is nausea and vomiting. Xylazine causes emesis by direct effect on α_2 and opiate receptors placed in CTZ of the area postrema. This effect can be very dangerous in small animal practice

because of increasing the risk of aspiration pneumonia.[2-4] New generation of α_2 agonists like detomidine and medetomidine is now available in market with less emetic effect. But clarification of inhibitory efficacy of different antiemetics which are acting via different receptors than α_2 receptors, can explain interaction of different receptors in vomiting centers which is so interesting in basic and clinical pharmacology of emesis.

Nausea and vomiting

Vomiting is the forceful expulsion of the stomach contents through the mouth and sometimes the nose.[15] Variety conditions like gastritis or poisoning can cause vomiting. Sometimes vomiting is a non-specific response of some disorders ranging from brain tumors and elevated intracranial pressure to overexposure to ionizing radiation. There are various sources of input to the vomiting center: 1) The chemoreceptor trigger zone at the base of the fourth ventricle, enriched with numerous dopamine D2 receptors, serotonin 5-HT_3 receptors, opioid receptors, acetylcholine receptors, and receptors for substance P. 2) The vestibular system, which transmit information from ear to the brain via cranial nerve VIII (vestibulocochlear nerve), and plays a major role in motion sickness, and is rich in muscarinic receptors and histamine H_1 receptors. 3) The Cranial nerve X (vagus nerve) is activated by pharynx irritation, leading to a gag reflex. 4) The Vagal and enteric nervous system send information regarding the state of the gastrointestinal system. 5) The CNS mediates vomiting that arises from psychiatric disorders and stressful conditions from higher brain centers.[16, 17] Vomiting can be very dangerous if the gastric content enters the respiratory system. Under normal conditions the gag and coughing reflexes prevent this from occurring; however these protective reflexes are abolished in animals under the influences of certain substances such as anesthesia which can be end up with aspiration pneumonia.

Xylazine induced emesis in cats

CTZ of cat is highly enriched in α_2 adrenoreceptors which make this animal sensitive to α agonist like adrenalin and noradrenalin which were produced in stress condition or medication like α_2 agonists such as xylazine. Xylazine induced emesis is mediated by α_2 adrenoceptor placed in CTZ of the area postrema.[2, 3]

Antiemetics

An antiemetic is a medication that is effective against nausea and vomiting. Antiemetics are used to prevent or treat motion sickness and the side effects of opioid analgesics, general anesthetics, chemotherapy directed against cancer and any other medications induced emesis like xylazine.[18] There are various antiemetics in practice which they have different mechanism of action and their effect is mediated via different receptors. Antiemetics include: 1) 5-HT_3 receptor antagonists: these block serotonin receptors in the central nervous system and gastrointestinal tract. They include: a) Dolasetron b) Granisetron c) Ondansetron d) Tropisetron e) Palonosetron f) Mirtazapine. 2) Dopamine antagonists block dopamine receptors in the brain and are used to treat nausea and vomiting associated with neoplastic disease, radiation sickness, opioids, cytotoxic drugs and general anesthetics. They include: a) Domperidone, b) Olanzapine, c) Droperidol, d) haloperidol, e) chlorpromazine, f) promethazine, g) prochlorperazine. Some of these drugs are limited in their usefulness by their extra-pyramidal and sedative side-effects. h) Metoclopramide as a pro-kinetic drug acts on the GI tract, and is thus useful in gastrointestinal disease3) neurokinin-1 (NK-1) receptor antagonist which include a) Aprepitant, b) Maropitant and c) Casopitant. 4) Antihistamines (H1 histamine receptor antagonists), with an expand effectiveness act in various conditions, including motion sickness, morning sickness in pregnancy, and opioid nausea. They include a) Cyclizine, b) Diphenhydramine, c) Dimenhydrinate, d) Doxylamine, e) Meclozine, f) Promethazineand g) Hydroxyzine. 5) Benzodiazepines which include a) Midazolam and b) Lorazepam which mostly effective in psychotic nausea and vomiting 7) Anticholinergics like a) Hyoscine (also known as scopolamine) 8) Steroids like a) Dexamethasone 9) Other miscellaneous antiemetics like a) Trimethobenzamide (thought to work on the CTZ), and b) Ginger (contains 5HT3 antagonists gingerols and shogaols).[14]

In this review, we will discuss these recent findings in which we will focus on the efficacy of prophylactic administration of different antiemetics which are acting via different mechanism (including neurotransmitters and receptors), in preventing vomiting in cats treated with xylazine hydrochloride.

Acepromazine

Acepromazine or acetylpromazine is a phenothiazine derivative antipsychotic drug. It is frequently used in animals as a sedative and antiemetic. Hikasa et al. have shown that acepromazine can inhibit emesis in cat via acting centrally on chemoreceptor trigger zone and vomiting center in the medulla oblongata as well as increasing gastric tone and peristalsis.[4]

Topal and Gul studied the effects of dexamethasone, metoclopramide and acepromazine on xylazine induced emesis in Cats. They injected antiemetic drugs in semitendinous muscle of one leg. Acepromazine was administered with relatively high dosage of 0.1 mg/kg. One hour later, each cat received xylazine (2 mg/kg, intramuscularly (IM)) in the semitendinous muscle of the other leg. They reported that acepromazine couldn't

reduce incidence of xylazine-induced emesis, but it was able to significantly increase latency time of emesis (time until onset of the first emetic episode). Furthermore, acepromazine at the studied dose did not alter the recumbency period induced by xylazine. The cats also experienced prolonged sedation period after administration of xylazine.[19] It has to be mentioned that the dose of xylazine in this study was higher than the other studies mentioned in this review.

Promethazine

It has been shown that prior treatment of cats with promethazine is effective in reducing the frequency of xylazine-induced emesis. 3 dosages of promethazine HCl (1, 2 and 4 mg/kg of body weight, IM) was injected an hour before administration of xylazine (0.66 mg/kg, IM) with one week intervals. Prior treatment with promethazine at dosages 2 and 4 mg/kg significantly reduced the number of episodes of emesis induced by xylazine. Promethazine did not alter the time until onset of the first emetic episode as well as the time to onset of sedation in xylazine injected cats. It is assumed that promethazine exerts its antiemetic action on xylazine induced emesis via inhibiting histamine and dopamine receptors of NTS rather than inhibition of α_2 adrenoceptors.[20]

Metoclopramide

Dopamine stimulates the medullary CTZ, producing nausea and vomiting. It has been shown that metoclopramide inhibits xylazine induced emesis in cats.[21] Five dosages of metoclopramide HCl (0.2, 0.4, 0.6, 0.8 and 1 mg/kg of body weight, IM) was evaluated against saline (0.9% NaCl) solution. Prior treatment with metoclopramide at any of mentioned dosages did not significantly alter the latency time of emesis in cats sedated with xylazine hydrochloride. But each dosage of metoclopramide significantly reduced the number of episodes of emesis in these cats. Results showed that 1 mg/kg of metoclopramide injected prior to administration of xylazine significantly reduced the time until onset of sedation in cats. Because of its antagonistic effect on dopamine and serotonin receptors, metoclopramide may complete its antiemetic action in xylazine induced emesis via inhibiting dopamine and serotonin ($5HT_3$) receptors in the bilateral NTS in this nervous pathway.

Ondansetron

5-HT3 receptors are found pre- and postsynaptically. Release of several neurotransmitters such as dopamine, cholecystokinin, GABA, substance P and acetylcholine is regulated by their activation.[22] 5-HT3 antagonists may have antiemetic effects in cats sedated with xylazine. It has been shown that ondansetron at dosages of 0.2, 0.4 and 0.8 mg/kg injected prior to administration of xylazine significantly reduced the number of episodes of emesis. Ondansetron may not inhibit α_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 $5\text{-}HT_3$ receptors of the area postrema.[23]

Dexamethasone

Several studies have suggested that glucocorticoids, such as dexamethasone, may be involved in the control of xylazine induced emesis.[19, 24, 25] After first report of dexamethasone as an effective antiemetic in cancer patients receiving chemotherapy[26] several studies have documented that dexamethasone is effective in preventing emesis caused by chemotherapy in humans,[27-29] cats,[30] dogs,[31] ferrets,[32, 33] and pigeons[34]. In a study by Topal and Gul, it was shown that Dexamethasone (4 mg/kg, IM), prevented xylazine (2 mg/kg, IM) induced vomiting in five of ten cats. Pre-treatment with dexamethasone also reduced incidence of vomiting induced by xylazine in the other five cats with no significant change in the time until onset of the first emetic episode.[19] This finding is in agreement with findings of Ho et al. (2001) which showed prior IM treatment with dexamethasone (4 or 8 mg/kg) significantly reduces the frequency of xylazine induced emesis. But they stated that dexamethasone significantly delays latency time of vomiting after xylazine injection in cats. It may be due to lower dose of xylazine (0.66 mg/kg) which has been used in their study. However, dexamethasone doesn't significantly change the time until onset of sedation after administration of xylazine.[24] Several authors have hypothesized that the bilateral NTS may be the common final pathway that links to the vomiting center.[35] Moreover, large numbers of glucocorticoid receptors are in the bilateral NTS.[36] Dexamethasone could ameliorate vomiting response through its action on glucocorticoid receptors in the bilateral NTS.[25]

Maropitant

Maropitant was highly effective in preventing motion induced emesis in cats at the dosage of 1 mg/kg. It is a NK-1 receptor antagonist that is well tolerated, safe and possesses excellent anti-emetic properties in cats. Provocative motion sickness needs the vestibular system, the signals from which finally activate brain stem areas involved in emesis including the NTS, the dorsal motor nucleus and an area adjacent to the area postrema.[37-39] Comparable to other anti-emetic agents, NK-1 receptor antagonists are effective against a wide range of emetogens including radiation, cisplatin, cyclophosphamide, copper sulfate and apomorphine as well as motion-induced emesis.[40-45] Such wide spectrum

activity against peripheral and central emetogens suggests that NK-1 receptor antagonists must have a site of action in a final common pathway of the emetic reflex. Maropitant effectively prevented xylazine (0.66 mg/kg) induced emesis in cats when administered at the dosage of 1 mg⁄kg via the subcutaneous, intravenous or per oral route 2 h before xylazine challenge; it could reduce the mean number of emetic episodes by 76, 100 and 90%, respectively, compared to untreated cats. Hickman et al. concluded that the site of the anti-emetic action of maropitant is most likely to be within the central nervous system.[46]

Vitamin B6

Vitamin B6 is a water-soluble B complex vitamin that is an essential coenzyme in the metabolism of amino acids, carbohydrates, and lipids.[47] It has been shown that vitamin B6 is an effective therapy for nausea and vomiting of pregnancy in humans.[48-50] Vitamin B6 is also commonly used as a first-line therapy for patients who experienced nausea and vomiting during or after chemotherapy,[51] and its safety has been proved when used in appropriate dose.[52, 53] The results of a recently published study indicated that pretreatment of cats with vitamin B6 at dosages of 5, 10, 20 and 40 mg/kg before injecting xylazine (0.66 mg/kg) could reduce episodes of emesis without any significant change in the time needed for sedation of cats after administration of xylazine.[54] Vitamin B6 may be used as a prophylactic antiemetic in cats treated with xylazine. As vitamin B6 administration increases central production of GABA,[55] it may exert its antiemetic action indirectly on vomiting center in medulla oblongata and block vomiting pathways via stimulating GABA receptors of the area postrema. It was shown that GABA receptors are abundant in the area postrema of the cat.[56] On the other hand, baclofen, a selective $GABA_B$ receptor agonist, has been shown to have direct inhibitory action in dorsal vagal complex (DVC) neurons in morphine-induced emesis in ferrets.[10] DVC in the brainstem regulates the emetic reflex in ferrets[57] and GABA mediates the inhibitory synaptic currents in these areas.[58]

Conclusion

As discussed briefly, all medications such as acepromazine, promethazine, metoclopramide, ondansetron, dexamethasone and vitamine B6 have been shown to have antiemetic efficacy on xylazine induced emesis in cats. These mentioned medications have different antiemetic mechanism of actions. It can be concluded that all these medications may exert their antiemetic effects directly on NTS and vomiting center (Fig 1).

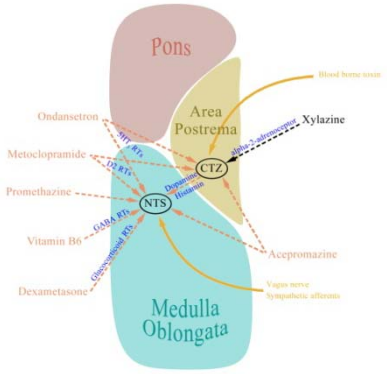

Figure1. Different antiemetics with different mechanism of actions may exert their antiemetic effects on xylazine induced emesis directly on NTS and vomiting center. "RTs" is abbreviation of "Receptors".

Abbreviations

CTZ: Chemoreceptor Trigger Zone; NTS: Nucleus Tractus Solitarius; GABA: Gamma-Amino Butyric Acid; CNS: Central Nervous System; IM: Intramuscularly; NK-1: neurokinin-1.

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چکیده

کارائی ضد استفراغ های متفاوت با مکانیسم متفاوت بر استفراغ ناشی از زایلازین هیدروکلراید در گربه

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زایلازین هیدروکلراید، آگونیست آلفا-۲ آگونیستی، یک داروی ضد درد، مسکن، آرام بخش و شل‌کننده عضلانی در دامپزشکی می‌باشد که بیشتر در پیش‌بیهوشی در دامپزشکی مورد استفاده قرار می‌گیرد. یکی از مهمترین اثرات جانبی زایلازین تهوع و استفراغ می‌باشد که استفاده از این دارو را در طب دامهای کوچک به خصوص گربه‌ها محدود می‌کند چرا که می‌تواند این اثر در نهایت به پنومونی استنشاقی منجر گردد. در این مقاله مروری، ما در مورد کارائی تجویز پیش‌گیرانه ضد استفراغ‌های مختلف با مکانیسم های اثر مختلف در پیش گیری از استفراغ ناشی از تجویز زایلازین هیدروکلراید در گربه بحث خواهیم کرد. کارائی تمامی داروهای ذکر شده مانند، آسه‌پرومازین، پرومتازین، متوکلوپرامید، اندانسترون، دگزامتازون، ماروپیتنت و ویتامین ب ۶ در مهار استفراغ ناشی از زایلازین هیدروکلراید در گربه ها مشخص گردیده است. داروهای مذکور دارای مکانیسم اثر ضد استفراغی متفاوتی می‌باشند. نتیجه‌گیری حاصل از این مقاله مروری نشان می‌دهد که نه تنها هیچ یک از داروهای مذکور اثر مهار استفراغ ناشی از زایلازین در گربه را با مهار گیرنده های آلفا ۲ به جای نمی‌گذارند بلکه این اثر ضد استفراغی آنها ناشی از اثر مستقیم آنها در هسته مسیر منزوی و مرکز استفراغ می باشد.

کلید واژگان: کارائی، استفراغ، گربه، زایلازین، ضد استفراغ