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ETI-385 as a Novel Anti-emetic Against Drug Induced Emesis

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Introduction

Drugs currently used to prevent emesis (nausea and vomiting) target only one or a few of the pathways used by emetic stimuli to trigger the reflex. Thus, an anti-emetic drug will only be effective against some stimuli. Prior work determined that 8-OH-DPAT (DPAT, a 5-HT_{1A} agonist) was a universally effective anti-emetic. Although DPAT prevented emesis, it also elicited an extreme anxiety response making it unsuitable for therapeutic use. Our laboratory tested a proprietary drug developed from DPAT, ETI-385, to successfully prevent emesis in musk shrews against chemotherapy, drug and motion stimuli. To meet FDA regulations, we are required to test ETI-385 in another species before taking the drug into clinical trials. Work at Epiomed Therapeutics used ETI-385 to successfully prevent emesis in cats using motion stimuli and found a separation between the anti-emetic and anxiety-producing doses.

Objectives

- Determine the efficacy of ETI-385 in preventing symptoms of emesis against a drug stimulus.
- Determine any adverse side effects

Methods

We determined a dose response curve for ETI-385 administered 20 min before 0.66 mg/kg of Xylazine administered subcutaneously (SC.) After Xylazine administration they were placed in a Plexiglas observation chamber. Once in the chamber, the animals were transported to our testing room for a 30 minute observation. After observation, the animals were transported to the housing room where they were released to their home cages. The animals were released to the common room after their behavior was determined to be suitable for interspecies interaction. All procedures approved by IACUC.

Drug

ETI-385 is a proprietary drug developed by Epiomed Therapeutics. ETI-385 is derived from DPAT, a 5-HT_{1A} agonist. The drug was prepared once every two weeks and refrigerated until dilution.

Subjects

6 female domestic cats aged six months were used. They were housed in an AAALAC approved facility on a 12hr light/dark cycle with free access to food and water. Before administration of drugs animals were housed overnight in cages.

Scoring

During observation the time of latency to first vomit was recorded. The animals were also scored for symptoms of both emesis and anxiety. Each symptom of emesis was assigned a point value. The total score values for each animal were combined. A high symptom score is indicative of nausea whether or not emesis occurs.

Symptom	Points
Salivation 1 (abundant saliva production)	1 point
Salivation 2 (thick, frothy saliva)	2 points
Salivation 3 (thick, stringy saliva)	4 points
Panting (quick, heavy breathing)	2 points
Defecation (no description needed)	8 points
Urination (no description needed)	8 points
Vomit 1 (no description needed)	16 points

Table 1. Emetic symptoms and their description.

Results

Emetic Response in Shrews

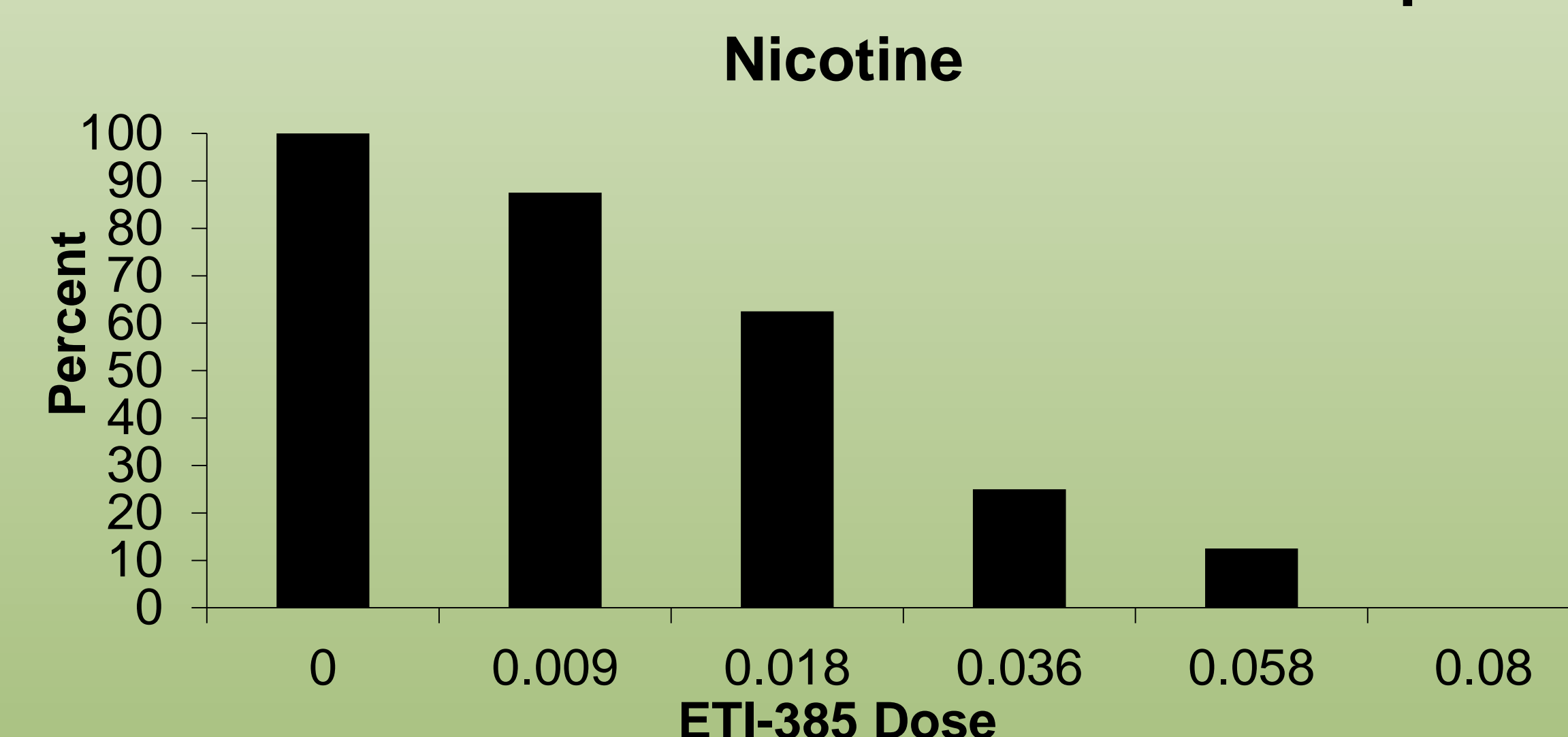


Figure 1. Percentage of shrews who vomited at each dose of ETI-385 against nicotine

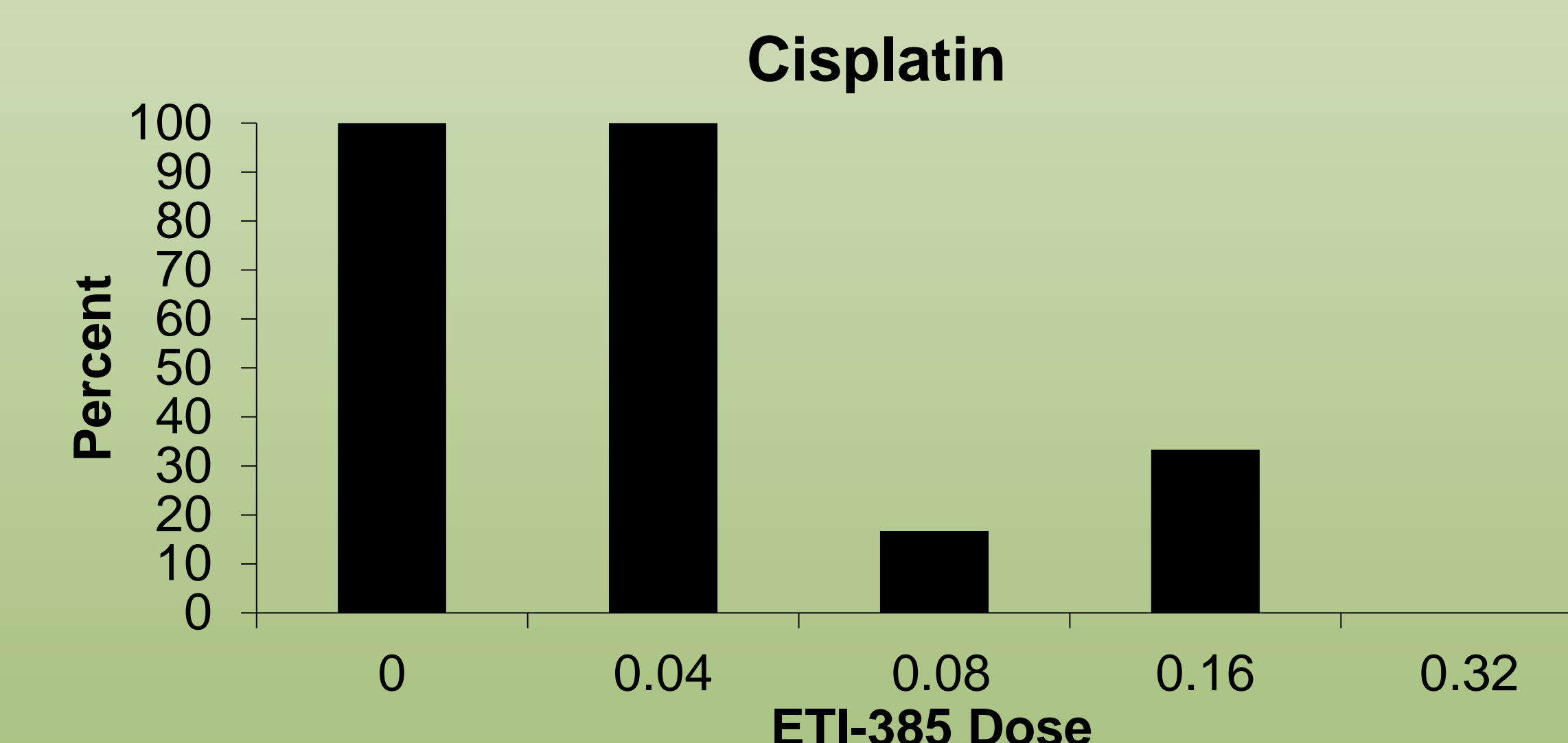


Figure 2. Percentage of shrews who vomited at each dose of ETI-385 against cisplatin.

Emetic Response in Cats

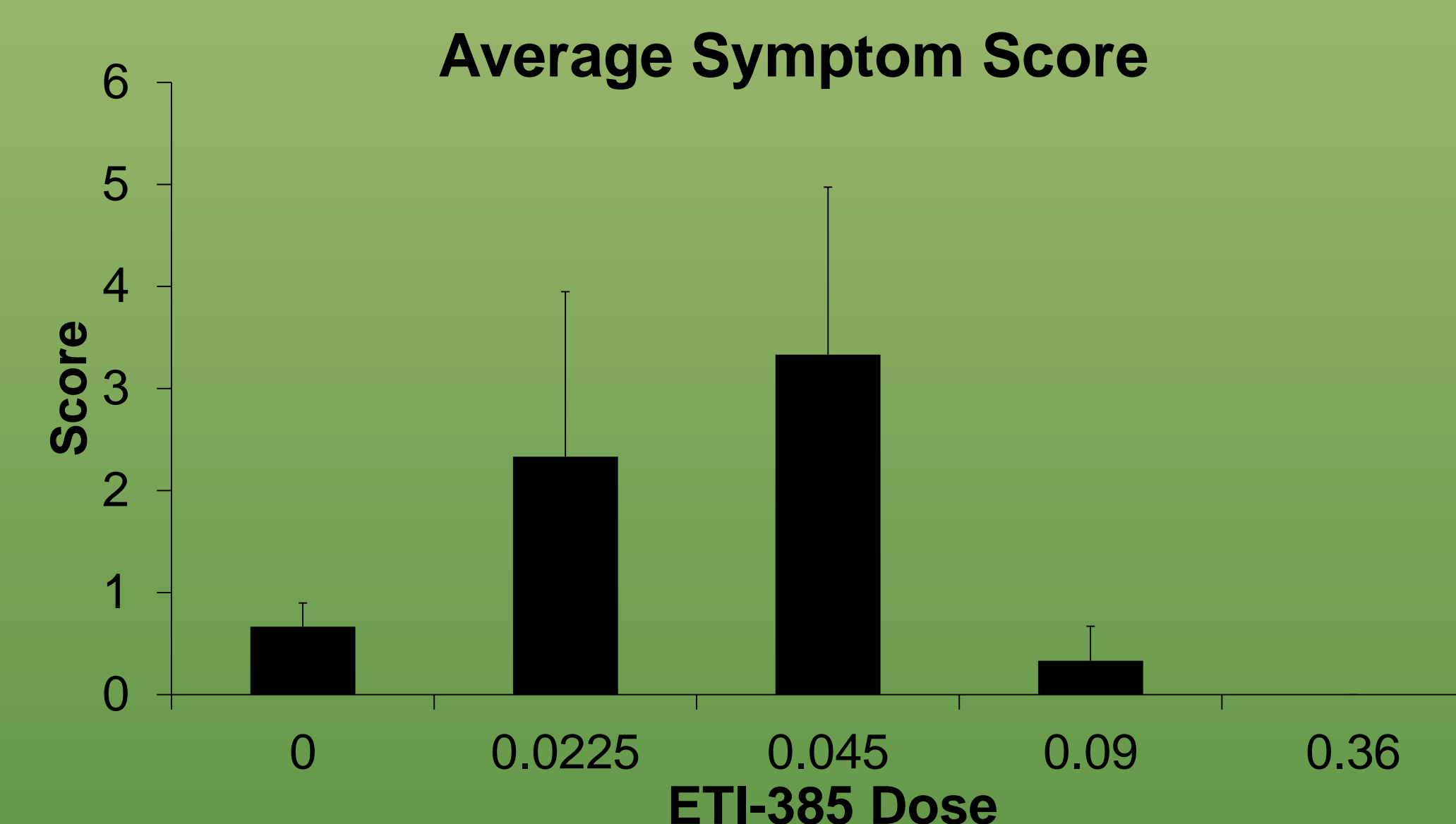


Figure 3. Average score after treatment with ETI-385 and Xylazine after subtracting 16 points for emesis.

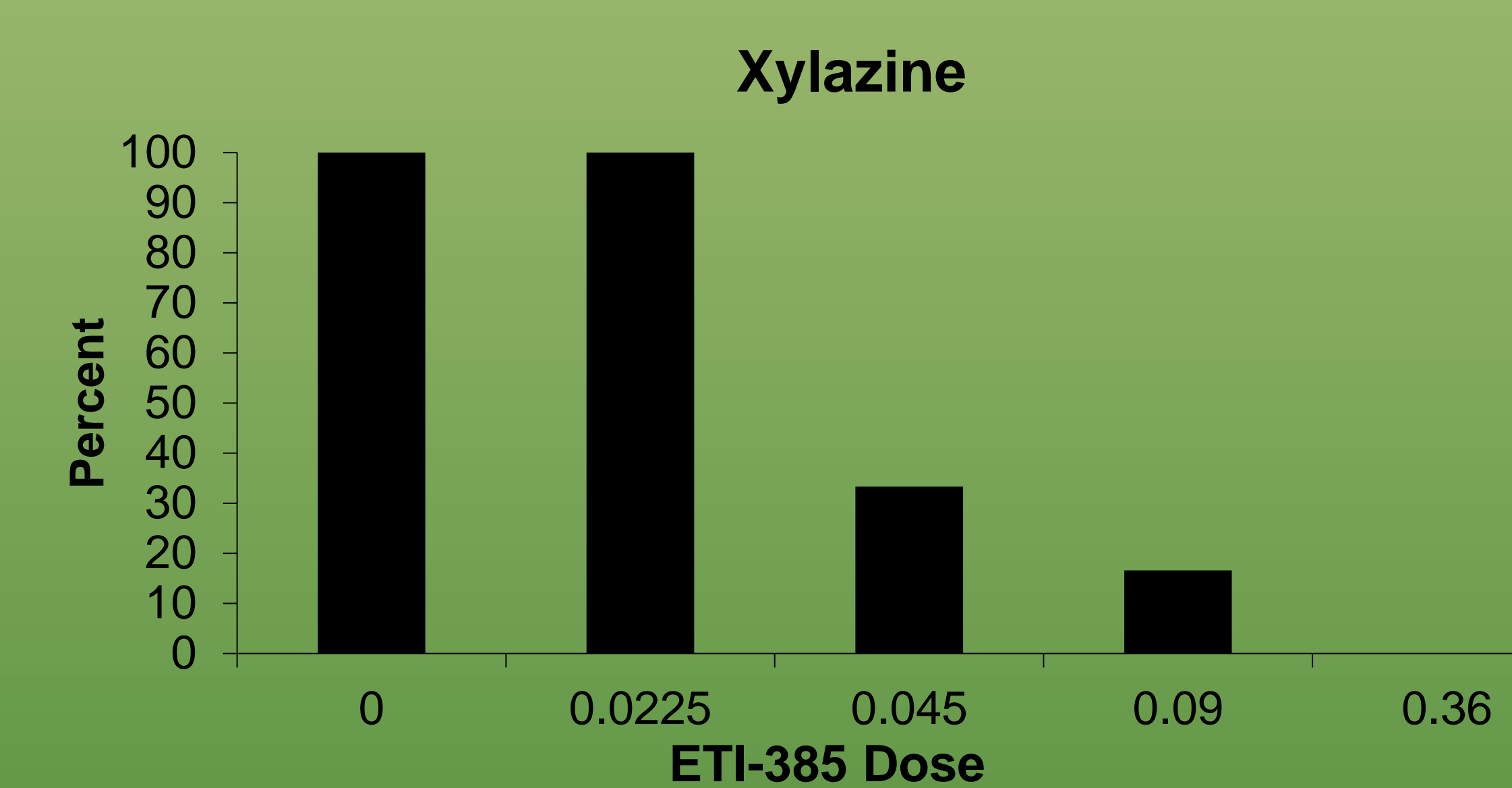


Figure 4. Percentage of cats who vomited at each dose of ETI-385 against Xylazine.

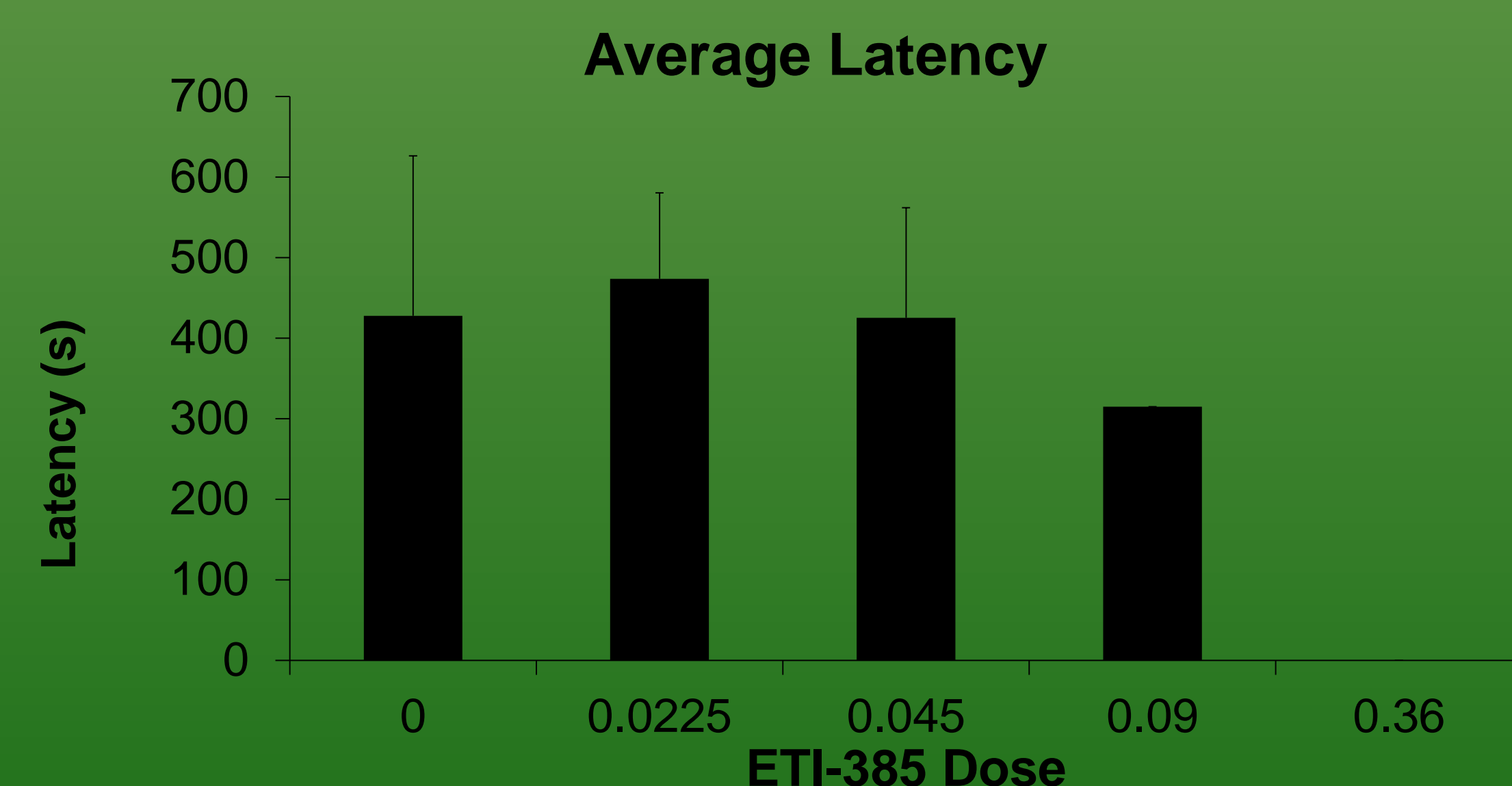


Figure 5. Latency to first vomit after treatment with ETI-385 and Xylazine.

Conclusion

- 0.0225mg/kg was unsuccessful in preventing emesis and produced a higher symptom score than Xylazine alone, suggesting nausea.
- 0.045mg/kg was 66.7% effective against vomiting but had an increase in symptom score
- 0.09mg/kg was 83.4% effective against vomiting with a marked decrease in symptom score.
- At the 0.36 mg/kg dose we achieved 100% efficacy and a complete eradication of emetic symptoms.
- Unlike DPAT, only the highest dose of ETI-385 produced any defensive behavior.