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Review

Effects of naloxone on motion sickness in cats alone and with broad spectrum antiemetics

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ABSTRACT

Doses of naloxone far below those which elicit emesis increase the sensitivity to motion sickness. In order to evaluate the possible interaction with broad spectrum antiemetics, low doses of naloxone were tested alone and in combination with 8-hydroxy-2-(di-n-propylamine)tetralin (DPAT), fentanyl and the NK1 antagonist CP-99994. A modified autonomic symptom rating scale was unaffected by any drug and thus considered of little value. Fentanyl and NK1 antagonists decreased the duration of the retch/vomit sequence. Naloxone alone and in combination with each of the drugs increased the duration of retching/vomiting. Naloxone also increased the number of vomiting sequences. The results are interpreted in terms of possible site(s) of action of the antiemetic drugs.

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1. Introduction

Emesis results from stimuli acting on specific pathways which converge in the vicinity of the nucleus tractus solitarius (NTS). From there, signals are sent to activate areas involved in nausea, autonomic nervous system (ANS) symptoms and the action of respiratory muscles to cause emesis (Yates et al., 2014). Nausea and ANS symptoms usually precede vomiting but either may consistently occur before the other and the ANS symptoms are consistently either sympathetic or parasympathetic (Cowings et al., 1990). To date, the opioids are the only drug class in clinical practice that can prevent emesis by all stimuli, which is an action separate from their ability to elicit emesis (Kakimoto et al., 1997; Barnes et al., 1991; Costello and Borison, 1977). This suggests

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that the relevant receptors are at some critical level of emetic pathway past those which carry the information from specific emetic stimuli. It has been proposed that the release of endogenous opioids may play a role in termination of the retch/vomit sequence (Lucot, 1997; Yates et al., 1998). The site of action has been proposed to be the nucleus tractus solitarius, where emetic pathways converge (Rudd et al., 1999). However, it could also include the respiratory nuclei which control emesis because opioid receptors are located in both areas (Sales et al., 1985).

This laboratory has often speculated about the functional location of broad spectrum antiemetic drugs based on their ability to decrease ANS symptoms or alter the duration of the retch/vomit sequence (e.g. Lucot and Crampton, 1989; Lucot et al., 1997). Tentative assignments to sites of functional components of the emetic sequence for 5-HT1A agonists, NK-1 antagonists and NMDA antagonists have been proposed (Lucot, 1998). This has been expanded to suggest anatomical sites of action as well (Yates et al., 1998). The speculations were testable by others with the suitable techniques. The present study was conducted to evaluate the actions of the only other broad spectrum antiemetic, the opioids, on the pattern of symptoms in the cat, including the duration of the retch vomit sequence. The duration of this sequence has not been altered by drugs in any of our published papers (Lucot, 1994). A preliminary report that agonism and antagonism of mu opioid receptors altered the duration of the retch vomit sequence (Lucot, 1997) led to the evaluation of the effects of naloxone on the other broad spectrum antiemetics with emphasis on the symptoms and duration of the sequence.

The role of antiemetic opioid receptors was probed by determining the minimum dose of the opioid antagonist naloxone that altered motion-induced emesis. This is important because high doses of naloxone are able to elicit emesis in several species (e.g. Rudd et al., 1999; Bhargava et al., 1981). A low dose administered before motion testing in human subjects decreased the latency to malaise (Allen et al., 1986). A previous effort to determine this dose in cats gave a fixed dose to all cats irrespective of body weight and administered it 60 min before testing (Crampton and Daunton, 1983), necessitating a systematic replication using current knowledge and procedures for the present study. This dose was then combined with antiemetics that are effective against multiple emetic stimuli and the pattern of symptoms and duration of retch/vomiting evaluated. The antiemetics included fentanyl, the 5-HT1A/1D agonist 8-hydroxy-2-(di-n-propylamine)tetralin (DPAT) (Lucot et al., 2014) and the NK1 antagonists CP-99994 and L-759274.

2. Materials and methods

2.1. Subjects

A total of 15 cats were housed in the AALAC approved University Laboratory Animal Resources facility. The procedures were approved by the University Animal Care and Use Committee and conform with the "Guidelines for the Use of Animals in Neuroscience Research" approved by the NIH "Guide for the Care and Use of Laboratory Animals," NIH Pub no. 85023 (revised 1985). All cats were tested to assure the presence of normal free-fall right and vestibule-ocular reflexes. Female cats were used exclusively because they tolerate long-term experiments better than males. There were a minimum of 10 cats and up to 12 in the testing of each drug. The testing was interspersed with other experiments from 1990 until 1996 with two of the cats present in all studies and others being removed and replaced with others.

2.2. Motion testing

Motion sickness was induced by a motor-driven device that resembled an amusement-park Ferris wheel. The cats rode in clear plastic boxes suspended from two 0.445 m arms that rotated about the central horizontal axis at 0.28 Hz (17 rpm) (Crampton and Lucot, 1985). Motion tests lasted for 30 min of rotation plus 1 min of observation at rest. Antiemetic drugs or vehicle were administered subcutaneously (SC) before motion. All tests were separated by at least 2 weeks to prevent the development of habituation (Crampton and Lucot, 1991). Symptoms were rated according the scale devised by Suri et al. (1979). This scale awards from 1 to 8 points for symptoms elicited by emetic stimuli and 16 points for retching/vomiting. To prevent the 16 points from obscuring the drug effects specifically on the ANS symptoms, it was omitted from the analysis in this study. The duration of the retch/vomit sequence was measured and converted to min. Sequences of retching and vomiting were considered a discrete bout when the sequences were separated by 30 s.

2.3. Procedure

The cats were group housed except for housing individually in stainless steel cages from 1600 h the previous day until 1600 h the day of testing to preclude drug effects on conspecific social interactions. All vomited on at least 3 of five biweekly screen tests and were considered susceptible to motion sickness. A motion test with saline preceded all drug tests. The pre- and post-saline tests are presented to demonstrate the absence of carry over effects. Their continued susceptibility was verified by monitoring these saline control tests to maintain the criteria of three responses of last five tests. Occasional tests were conducted with saline administration and placing in the immobile testing device to probe for conditioned responses.

2.4. Drugs

Fentanyl (0.003–0.03 mg/kg, $N = 10$) was obtained under the supervision of the Animal Facility veterinarian. Naloxone (0.001–0.1 mg/kg, $N = 10$) and DPAT (0.4 mg/kg, $N = 12$) were purchased from Sigma Aldrich (St. Loius, MO). CP-99994 (0.17 mg/kg, $N = 10$) was a gift from Pfizer Pharmaceuticals and L759274 (0.3–3 mg/kg, $N = 12$) was a gift from Merck Sharp and Dohme Corp.

All drugs were dissolved in sterile saline to a concentration that would provide the proper dose in a volume of 0.1 ml/kg. Injections were SC on alternate sides of the nape of the neck. Pretreatment times were: naloxone, 10 min; CP-99994 and L759274, 30 min; DPAT 15 min; fentanyl, 5 min. Animals were returned to the cage until the time of testing and after testing, were cleaned if necessary and returned to the individual housing.

2.5. Statistics

Data were analyzed using either Statistica (Statsoft) or SPSS (IBM). Binomial data were analyze using Cochran Q test. The nonparametric rating scale was analyzed using Friedman ANOVA and Kendall Coefficient of Concordance. Duration data were analyzed using a repeated measures ANOVA on cats vomiting on all test in a drug series with a minimum of 4 meeting this criteria. Tukey's test was used after significant F values to determine differences between treatments.

3. Results

3.1. Fentanyl

Fentanyl produced a dose-dependent decrease in the number of cats vomiting (Table 1; $Q_4 = 16.8$, $p < 0.01$). There was no significant decrease in the number points ($\times^2_4 = 8.6$, $p = 0.07$) but there was a dose-dependent decrease in the duration of the retch/vomit sequence ($F_{3,27} = 4.02$, $p < 0.05$). An additional test was conducted with fentanyl administered before placing in the device without motion to probe for emetic effects. Neither vomiting nor symptoms were produced.