Pharmacology Biochemistry & Behavior, Vol. 19, pp. 827–829, 1983.

Systemic Naloxone Increases the Incidence of Motion Sickness in the Cat

GEORGE H. CRAMPTON

Department of Psychology, Wright State University, Dayton, OH 45435

AND

NANCY G. DAUNTON

Biomedical Research Division, NASA-Ames Research Center, Moffett Field, CA 94035

Received 5 May 1983

CRAMPTON, G. H. AND N. G. DAUNTON. *Systemic naloxone increases the incidence of motion sickness in the cat.* PHARMACOL BIOCHEM BEHAV **19**(5) 827–829, 1983.—Subcutaneous injections of naloxone in a total dose of 0.4 mg or greater one hour before a swing stimulus increased the frequency of motion sickness symptoms and shortened the latency to retching and vomiting.

Motion sickness Emesis Naloxone

ADMINISTRATION of morphine elicits emesis in man [18], dog [8], and cat [6]. The incidence is increased if a person is allowed to ambulate [5] or subjected to vestibular stimulation [13]. Intracerebroventricular (ICV) injection of the opiate antagonist naloxone prevents emesis following ICV administration of morphine in the cat [6], and intravenous (IV) naloxone blocks subcutaneous (SC) morphine-induced emesis in the dog [8]. Vomiting also follows ICV administration of the endogenous opiate met-enkephalin in the dog, and further, ICV pretreatment with naloxone protects against this enkephalin induced emesis [1]. These results suggest the possibility that endogenous opiates could be involved in the etiology of motion sickness, and if so, naloxone might alleviate the malady. Accordingly, the effects of systemic naloxone on motion sickness were investigated in this study.

METHOD

Subjects and Apparatus

Twenty female cats were tested individually in a clear plastic box with inside dimensions of 0.5×0.17×0.24 m. The box was oscillated on a two-pole swing having a radius of 3.7 m, a vertical displacement of 1.0 m, a frequency of 0.27 Hz, and an arc of 1.54 radians.

Response Measure

The latencies to the beginning of retching were noted to the closest 0.1 min. Latency to retching was selected as the dependent variable because the postural and motor responses were readily observed. Vomiting nearly always accompanied retching, but at longer latencies. Duration of the swing stimulus was 20.0 min, or time to retching/vomiting plus 5.0 min whichever was longer. This timing schedule was adopted so that cessation of swinging would not follow retching/vomiting for at least 5.0 min, thus reducing the possibility that animals might learn to retch or vomit in order to terminate the stimulus.

Test Schedule

Cats were tested on eleven occasions; each test separated by not fewer than ten intervening days. Each animal was tested at each drug level, and every test was preceded and followed by a control test. Four different sequences were used, as shown below, with five cats assigned to each sequence. Control tests are indicated by "C," and the numbers indicate the dosage in mg for the drug tests.

C; 0.2; C; 0.1; C; 0.8; C; 1.6; C; 0.4; C
C; 0.4; C; 0.2; C; 0.1; C; 0.8; C; 1.6; C
C; 0.8; C; 1.6; C; 0.4; C; 0.2; C; 0.1; C
C; 1.6; C; 0.4; C; 0.2; C; 0.1; C; 0.8; C

Drugs

For the drug tests, naloxone HCl (Narcan, Endo Laboratories, Inc., expressed as the weight of the salt) was administered SC 60 min prior to swinging in total doses of 0.1, 0.2, 0.4, 0.8 or 1.6 mg. The average weight of the cats was 2.9 kg. For control tests, 1.0 ml of physiological saline was administered SC 60 min prior to swinging.

RESULTS

Figure 1 shows the mean latencies to vomiting/retching within 20.0 min on each trial. Data are plotted in "triplets" with each drug level preceded and followed by the control test data. Averaged control data, except for the first and last test of the sequence, are therefore shown twice in the graph but only once for each triplet.

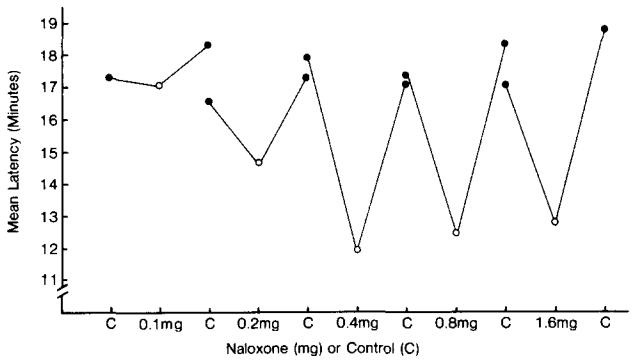

FIG. 1. Mean latency in minutes to vomiting or retching within a 20 min test period. Each data point represents the average for all 20 animals. Every drug test (indicated by mg of total dose) was preceded and followed by a control test indicated C.

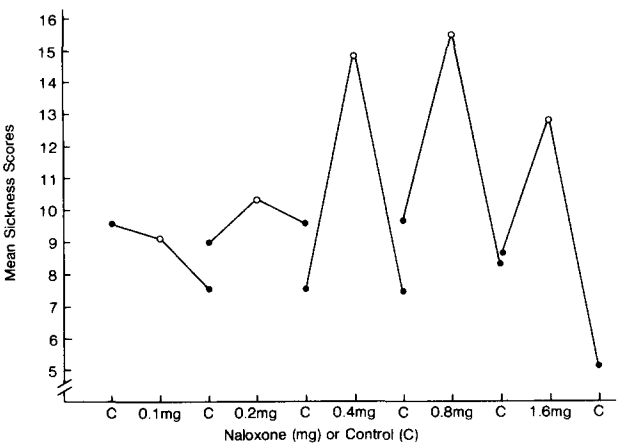

FIG. 2. Mean motion sickness scores within a 20 min test period plotted as in Fig. 1.

Tests of significance between latencies were made for each triplet and are listed in Table 1. The table shows unequivocally that naloxone in the 0.4–1.6 mg total dose range significantly decreased the latency to retching/vomiting. There were no significant correlations ($p<0.05$) between latencies and body weights within any of the dose levels.

In four of the five triplets, the mean latency of the post-drug control test was slightly longer than that for the pre-drug control test, indicating a modest habituation. Control test data were sorted into the order of presentation, and a least-squares linear fit confirmed that mean latencies were lengthened at a rate of 0.64 min per control test.

Supplementary Observations

The effects of naloxone were also evaluated using the symptom rating scale developed by Suri, Crampton and Daunton [14]. The scale score is the sum of arbitrarily assigned values for the symptoms of salivation, urination, defecation and retching/vomiting occurring during the test period. These scores, presented in Fig. 2 and Table 2, further confirm that naloxone increased the severity of motion sickness.

TABLE 1

VALUES OF t FOR DATA SHOWN IN FIG. 1

Dose	Pre-test vs. drug test	Post-test vs. drug test	Pre-test vs. post-test
0.1	0.227	1.130	1.363
0.2	0.740	1.872	0.693
0.4	3.705*	3.102*	1.062
0.8	3.594*	4.243*	1.290
1.6	3.124*	3.567*	1.774

*Significant at 0.01 level (two-tailed test).

TABLE 2

VALUES OF t FOR DATA SHOWN IN FIG. 2

Dose	Pre-test vs. drug test	Post-test vs. drug test	Pre-test vs. post-test
0.1	0.247	1.079	2.039
0.2	0.529	0.308	0.462
0.4	2.861†	2.854*	0.034
0.8	2.725*	2.873†	0.918
1.6	3.092†	3.910†	1.929

*Significant at 0.05 level (two-tailed test).
†Significant at 0.01 level (two-tailed test).

DISCUSSION

There are several possible explanations for the unexpected finding that naloxone exacerbates motion sickness. First, this drug is known to increase neural sensory input [3] and thus may intensify vestibular and other [7] inputs of importance to motion sickness.

A second possible explanation derives from the fact that systemic naloxone in very high doses is an emetic itself, not even requiring the chemical trigger zone in the area postrema [1,6]. Thus, naloxone may simply provide a chemical emetic stimulus that is synergistic with the motion sickness stimulus. It has been reported that naloxone alone rarely elicits vomiting even with an intraperitoneal dose of 5.0 mg/kg which is ten times the SC premedication used here [6]. By comparison, naloxone does cause emesis 80% of the time with ICV doses of 1.0 mg in the cat [6], and always with 0.16 mg ICV in the dog [1]. Such findings indicate that SC naloxone at the levels used in this experiment was substantially below the systemic threshold dose required to elicit vomiting. Emesis did occur three times in these 100 drug tests after injection and before vestibular stimulation commenced, and even though vomiting for no apparent reason is observed occasionally in cats, the possibility cannot be excluded that high motion sickness rates were the result of the additive effect of two emetic factors, naloxone and motion.

Another possibility is that the enkephalins modulate the production or reception of a mediator important to motion sickness. For example, dopamine (DA) is but one of many putative mediators. Intraventricular DA will elicit emesis in

dogs [9], and DA antagonists such as domperidone relieve nausea and vomiting in patients with Parkinson's disease receiving levodopa therapy [2]. Dopamine is found in the cerebrospinal fluid [16], and DA receptors are found in the area postrema (AP) [15]. Although it has not been demonstrated specifically that the AP is required for DA-induced emesis, the AP has been shown to be necessary for both dopa-induced vomiting [12] and motion sickness [17]. Important for the dopamine mediator hypothesis are the facts that DA production is modulated in part by vestibular stimulation [10] as well as by the endogenous opiates [4], and that the responsiveness of DA neurons is increased by naloxone [11].

The fact that latencies to vomiting increased slightly from control trial to control trial indicates that habituation was taking place over the course of the experiment. This small increase does not negate the results of the main effect, but is interesting because a ten-day interval was sufficient to prevent habituation in a previous experiment in which scopolamine was administered on alternate tests [14]. The different stimulus, different sickness rates, and perhaps subtle drug effects might account for the weak trend of habituation found in this experiment.

In summary, it is clear that naloxone increases feline susceptibility to motion sickness. The activities and effects of naloxone and the endogenous opiates are so ubiquitous as to leave the mechanism a matter of speculation until further clarification of the effects of naloxone is available.

ACKNOWLEDGEMENTS

The experimental work was performed at Wright State University in accordance with NASA-Ames University Consortium Interchange No. NCAZ-OR875-002. The authors acknowledge the fine technical assistance of Denise L. Dodson, William J. Green, Deborah L. Harm and Leslie A. Seiger. We thank Endo Laboratories, Inc., for donating naloxone.

REFERENCES

1. Bhargava, K. P., K. S. Dixit and Y. K. Gupta. Enkephalin receptors in the emetic chemoreceptor trigger zone of the dog. *Br J Pharmacol* **72:** 471–475, 1981.
2. Bogaerts, M., M. Braems and C. Martens. Domperidone in the prevention of L-dopa induced nausea. *Postgrad Med J* **55:** Suppl 1, 51, 1979.
3. Buchsbaum, M. S., G. C. Davis and W. E. Bunny, Jr. Naloxone alters pain perception and somatosensory evoked potentials in normal subjects. *Nature* **270:** 620–622, 1977.
4. Chesselet, M. F., A. Cheramy, T. D. Reisine and J. Glowinski. Morphine and delta-opiate agonists locally stimulate in-vivo dopamine release in cat caudate nucleus. *Nature* **291:** 320–322, 1981.
5. Comroe, J. H., Jr. and R. D. Dripps. Reactions to morphine in ambulatory and bed patients. *Surg Gynecol Obstet* **87:** 221–224, 1948.
6. Costello, D. J. and H. L. Borison. Naloxone antagonizes narcotic self-blockade of emesis in the cat. *J Pharmacol Exp Ther* **203:** 222–230, 1977.
7. Crampton, G. H. and F. A. Young. The differential effect of a rotary visual field on susceptibles and nonsusceptibles to motion sickness. *J Comp Physiol Psychol* **46:** 451–453, 1953.
8. Lefebure, R. A., J. L. Willems and M. G. Bogaert. Gastric relaxation and vomiting by apomorphine, morphine and fentanyl in the conscious dog. *Eur J Pharmacol* **69:** 139–145, 1981.
9. Lotti, V. J. and C. Clark. Carbidopa attenuation of L-dopa emesis in dogs: evidence for a cerebral site of action outside the blood-brain barrier. *Eur J Pharmacol* **25:** 322–325, 1974.
10. Maiti, A. K. Vestibulo-cerebellum modulates nigrostriatal dopamine synthesis: clinical implications in Parkinsonism. *Neuroendocrinol Lett* **4:** 196, 1982.
11. Neff, N. H., M. Parenti, S. Gentlemen and M. C. Olianas. Modulation of dopamine receptors by opiates. In: *Apomorphine and Other Dopaminomimetics,* vol II. edited by G. L. Gessa and G. U. Corsini. New York: Raven Press, 1981, pp. 193–200.
12. Peng, M. T. Locus of emetic action of epinephrine and dopa in dogs. *J Pharmacol Exp Ther* **139:** 345–349, 1963.
13. Rubin, A. and J. Winston. The role of the vestibular apparatus in the production of nausea and vomiting following the administration of morphine to man. *J Clin Invest* **20:** 1261–1266, 1950.
14. Suri, K. B., G. H. Crampton and N. G. Daunton. Motion sickness in cats: A symptom rating scale used in laboratory and flight tests. *Aviat Space Environ Med* **50:** 614–618, 1979.
15. Stefanini, E. and Y. Clement-Cormier. Detection of dopamine receptors in the area postrema. *Eur J Pharmacol* **74:** 257–260, 1981.
16. Von Voigtlander, P. F. and K. E. Moore. The release of H^3 dopamine from cat brain following electrical stimulation of the substantia nigra and caudate nucleus. *Neuropharmacology* **10:** 733–741, 1971.
17. Wang, S. C. and H. I. Chinn. Experimental motion sickness in dogs. Funcional importance of chemoreceptive emetic trigger zone. *Am J Physiol* **178:** 111–116, 1954.
18. Wangeman, C. P. and M. H. Hawk. The effects of morphine, atropine and scopolamine on human subjects. *Anesthesiology* **3:** 24–36, 1942.