AD-A201 972 | REPORT DOCUMENTATION PAGE

1b. RESTRICTIVE MARKINGS	DTIC FILE COPY

2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	Approved for public release; distribution unlimited.

4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
SR88-20	

6a. NAME OF PERFORMING ORGANIZATION	6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
Armed Forces Radiobiology Research Institute	AFRRI	

6c. ADDRESS (City, State and ZIP Code)	7b. ADDRESS (City, State and ZIP Code)
Defense Nuclear Agency Bethesda, Maryland 20814-5145	

8a. NAME OF FUNDING/SPONSORING ORGANIZATION	8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
Defense Nuclear Agency	DNA	

8c. ADDRESS (City, State and ZIP Code)	10. SOURCE OF FUNDING NOS.			
	PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT NO.
Washington, DC 20305	NWED QAXM			

11. TITLE (Include Security Classification)
(see cover)

12. PERSONAL AUTHOR(S)
Dubois, A., and Fiala, N.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Yr., Mo., Day)	15. PAGE COUNT
Reprint	FROM _____ TO _____	1988 November	10

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB. GR.	

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

DTIC
S ELECTE
DEC 23 1988
E D

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS ☐	

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE NUMBER (Include Area Code)	22c. OFFICE SYMBOL
M. E. Greenville	(202) 295-3536	ISDP

DD FORM 1473, 83 APR   EDITION OF 1 JAN 73 IS OBSOLETE.   UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

Prevention and Treatment of the Gastric Symptoms
of Radiation Sickness

ANDRE DUBOIS AND NANCY FIALA

*Laboratory of Gastrointestinal and Liver Studies, Digestive Diseases Division, Department of Medicine,
Uniformed Services University of the Health Sciences, and Department of Physiology, Armed Forces
Radiobiology Research Institute, Bethesda, Maryland 20814*

AND

CHESTER A. BOWARD AND VICTOR BOGO

*Department of Behavioral Sciences, Armed Forces Radiobiology Research Institute,
Bethesda, Maryland 20814*

DUBOIS, A., FIALA, N., BOWARD, C. A., AND BOGO, V. Prevention and Treatment of the
Gastric Symptoms of Radiation Sickness. *Radiat. Res.* 115, 595–604 (1988).

Currently available treatments for radiation-induced nausea and vomiting either are ineffective or reduce performance. The new antiemetic and gastrokinetic agent zacopride was tested in rhesus monkeys to assess its behavioral toxicity and its ability to inhibit radiation-induced emesis. Zacopride (intragastric, 0.3 mg/kg) or a placebo was given blindly and randomly in the basal state and 15 min before a whole-body 800 cGy ^{60}Co γ-radiation dose (except for the legs which were partially protected to permit survival of some bone marrow). We determined (1) gastric emptying rates; (2) the presence and frequency of retching and vomiting; and (3) the effect of zacopride on the performance of a visual discrimination task in nonirradiated subjects. No vomiting, retching, or decreased performance was observed after either placebo or zacopride in the control state. Following irradiation plus placebo, 70 emeses were observed in 5 of 6 monkeys, and 353 retches were observed in all 6 monkeys. In contrast, only 1 emesis was observed in 1 of 6 monkeys and 173 retches were seen in 4 of 6 monkeys after irradiation plus zacopride ($P < 0.01$). Zacopride also significantly inhibited radiation-induced suppression of gastric emptying. When given after the first vomiting episode in a separate group of irradiated monkeys, zacopride completely prevented any subsequent vomiting. The present results demonstrate that intragastric administration of zacopride significantly inhibited radiation-induced retching, vomiting, and suppression of gastric emptying in rhesus monkeys and did not cause detectable behavioral side effects when given to nonradiated monkeys. This observation has important implications in the treatment of radiation sickness. © 1988 Academic Press. Inc.

INTRODUCTION

Therapeutic and accidental exposure to doses of radiation greater than 150 cGy causes nausea, vomiting, and suppression of gastric emptying in man, monkeys, and dogs (*1–4*). In addition, the normally low doses of radiation that may be encountered in space could play a role in the man–space program, because some of the symptoms observed in space sickness and radiation sickness are similar (*5*). Medications cur-

rently available to treat radiation- and space-induced nausea and vomiting either are ineffective or reduce performance ability. For example, we previously reported (4, 6) that metoclopramide, but not domperidone, effectively prevents radiation-induced vomiting in rhesus monkeys. However, metoclopramide is known to cause involuntary movements in treated patients (7).

Recently, several benzamide derivatives of the metoclopramide class have been introduced for the treatment of emesis and/or gastroparesis, and these derivatives may not have behavioral side effects. Therefore, we evaluated the action of one of these agents, zacopride, on radiation-induced vomiting and gastric suppression in rhesus monkeys. Specifically, we studied the possibility of preventing and treating radiation-induced vomiting and suppression of gastric emptying using zacopride. We also determined the possible side effects of this therapeutic agent on gross behavior and on performance of a visual discrimination task.

MATERIAL AND METHODS

Twenty-four male domestic rhesus monkeys, *Macaca mulatta,* mean weight 3.1 ± 0.2 kg, were used in these experiments. Monkeys were quarantined on arrival and screened for evidence of disease before being released from quarantine. They were maintained in an AALAC accredited facility and were held in individual stainless steel cages in conventional holding rooms maintained at $21 \pm 1°C$ with $50 \pm 10\%$ relative humidity. Animals were on a 12-h light/dark full-spectrum lighting scale with no twilight and were provided with tap water *ad libitum,* commercial primate chow, and fruits.

After adaptation to a primate-restraining chair, six monkeys were trained to discriminate between a circle and a square (correct) randomly presented every 10 s on backlit press-plates, mounted on an eye-level response panel (8). An incorrect response or failure to respond within 0.8 s resulted in a 3-mA shock. Incoming efficiency on the visual discrimination task was $97 \pm 2\%$ in the six monkeys. Percentage correct choice was assessed during 18 min (100 trials) before, and for 180 min (1000 trials) after, oral administration of a placebo or zacopride (AHR 11190B, A. H. Robins Co, Richmond, VA). A repeated measure design was used as follows: (a) baseline control without oral administration of fluid; and (b) blind administration of either 0.3 mg/kg zacopride in 5% glucose solution or 0.2 ml/kg of 5% glucose solution.

Twelve other chair-adapted monkeys were studied on 3 separate days after an overnight fast as follows: (1) and (2) on two control days after random and blind intragastric administration of either placebo (0.2 ml/kg) or zacopride (0.3 mg/kg), and (3) on irradiation day after intragastric administration of either placebo or zacopride given blindly and in random order 15 min before exposure. These doses of zacopride were selected based on previous monkey experiments (unpublished observations) demonstrating that these doses did not produce noticeable side effects. Studies were performed in the morning and started 30 min after drug administration and 15 min after either sham-radiation (on control days) or radiation exposure.

On control days, the animals were brought to the exposure room and the doors were closed for 3 min, but no radiation was delivered. On irradiation day, monkeys were placed between two large, 10^5-Ci ^{60}Co irradiators, and the animals received nonuniform radiation exposure through positioning of lead wall shields in front of and behind their legs (9). Phantom studies demonstrated that a 1-min exposure resulted in midtissue doses of 800 cGy for torso and abdomen, 896 cGy for head, 584 cGy for femurs, and 425 cGy for tibiae (9).

The six remaining monkeys were studied once in the basal state without treatment and again after irradiation as described above but without drug administration prior to exposure. After one episode of vomiting had occurred, 0.3 mg/kg zacopride was given intragastrically, and the study was performed as described above. If vomiting recurred again within 3 min of zacopride administration, a second dose of medication was administered.

Each monkey was monitored for 3 h on control days and 6 h on irradiation days using a videocamera and a video cassette recorder. The videotapes were blindly evaluated at a later time for vomiting, retching, and any other side effect. During this evaluation, vomiting was defined as a succession of strong and brief contractions of thoracic and abdominal muscles leading to the expulsion of gastric contents through the mouth; retching was defined as nonproductive vomiting (4).
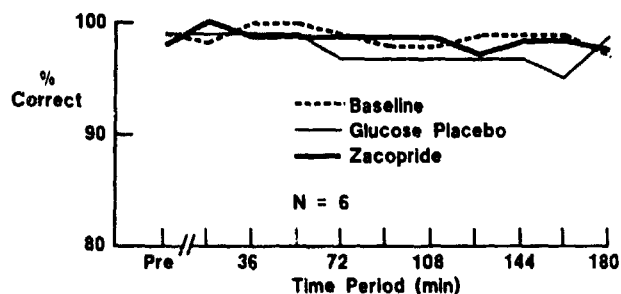
FIG. 1. Effect of zacopride on visual discrimination performance. Six monkeys were tested repeatedly at 2-week intervals without treatment (baseline), after oral placebo, and after oral zacopride administration (0.3 mg/kg).

A previously described and validated marker dilution technique (10) was used to determine concurrently gastric secretion and gastric emptying during a 40-min fasting period and for 60 min after the injection of an 80-ml water meal (postmeal period). In the present studies, as previously reported (4), this technique was slightly modified in that [^{99m}Tc]DTPA (diethylenetriamine pentacetic acid) was used as the marker instead of phenol red. This intubation method requires only the sequential sampling of the gastric contents, and it permits the concurrent measurement of intragastric volume, gastric emptying, and gastric secretion. A 12-French double lumen nasogastric tube was placed in the stomach and its position was verified by the water recovery test (11). Starting 45 min later, samples of the mixed gastric contents were aspirated just before and immediately after intragastric administration of 5 to 20 ml of a [^{99m}Tc]DTPA test solution (30 μCi/100 ml H$_2$O; pH 7.4; 37°C). After centrifugation of the samples, the clear supernatants were assayed for ^{99m}Tc concentrations using an autogamma counter (1282 Compugamma LKB Instruments, Inc., Gaithersburg, MD). These determinations were repeated every 10 min during the basal period and after intragastric instillation of an 80-ml water meal containing [^{99m}Tc]DTPA (3 μCi/100 ml; pH 7.4; 37°C).

Intragastric volumes of fluid (V_1, V_2, · · ·) and amounts of ^{99m}Tc (Tc$_1$, Tc$_2$, · · ·) were determined at the time of each sampling using the marker dilution principle (4, 10, 12, 13). Fractional emptying rate (g) was then determined for each 10-min interval (t) between two dilutions, assuming that emptying was a first-order process (exponential) during a given 10-min interval. However, since g was allowed to vary from interval to interval, no general assumption was required regarding emptying over the total duration of the experiment. We used the following equation:

$$g = -[\log_e(Tc_2/Tc_1)]/t.$$

Net fluid output (R_v) in milliliters per minute was then determined for the corresponding interval, assuming that R_v remained constant over the given interval and using the equation:

$$R_v = [V_2 - V_1 \cdot \exp^{-gt}] \cdot g/[1 - \exp^{-gt}].$$

Intragastric volumes of fluid and masses of ^{99m}Tc were then recalculated, taking into account these first estimates of fractional emptying and fluid output, which were in turn recalculated. This iterative process was repeated until the improvement of the solution was less than 1% per iteration.

These calculations were performed using a locally developed program and a PDP-10 computer (Division of Computer Research and Technology, National Institutes of Health, Bethesda, MD). The assumptions involved have been described and discussed elsewhere (10) and are based on original contributions by Hildes and Dunlop (12) and George (13). However, in contrast to their method, the present technique allows correction for emptying and secretion that occur during the 1-min marker dilution interval, and this technique can be applied during fasting. On irradiation day, intervals with occurrence of vomiting were not taken into account for calculation of g and R_v.

Statistical evaluation of visual-discrimination performance data was assessed using a two-way analysis of variance. The statistical significance of differences observed for fractional emptying rate and fluid output was evaluated using a three-factor (treatment, time, and monkey) analysis of variance with repeated mea-
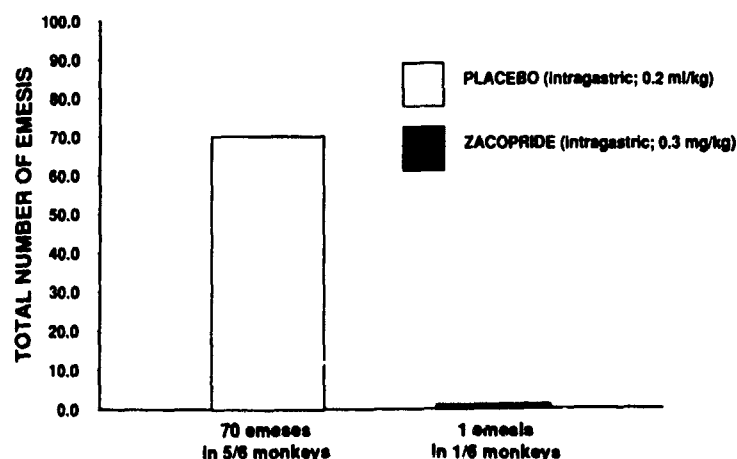
FIG. 2. Effect of zacopride on the total number of radiation-induced emeses. Placebo or zacopride was given intragastrically 30 min before irradiation, and the number of emeses was determined using a videotape. Emesis was defined as a succession of strong and brief contractions of thoracic and abdominal muscles leading to expulsion of gastric contents through the mouth.

sures on the last two factors (*10*). This was done using the program LDU-040 (K. L. Dorn) and an IBM 370 computer (Division of Computer Research and Technology, National Institutes of Health, Bethesda, MD). For vomiting and retching data, statistical analysis was performed using the Behrens-Fisher test (*14*).

RESULTS

No vomiting, retching, or other side effects were observed after placebo alone or zacopride alone. Similarly, zacopride did not significantly modify performance as assessed with a visual discrimination task in nonirradiated animals (Fig. 1).
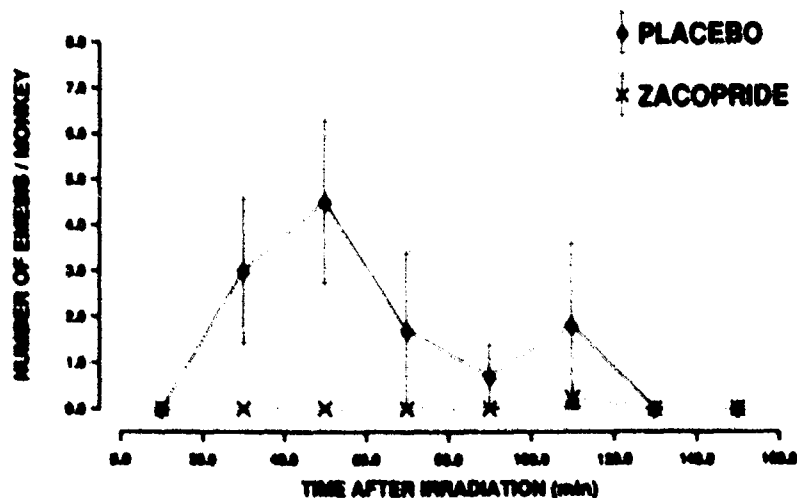

FIG. 3. Effect of zacopride on time course of radiation-induced emesis. Placebo or zacopride was given intragastrically 30 min before irradiation. The number of emeses as determined using a videotape w·· averaged for each 20-min period. Emesis was defined as a succession of strong and brief contractions of thoracic and abdominal muscles leading to the expulsion of gastric contents through the mouth. Values are means ± SE.
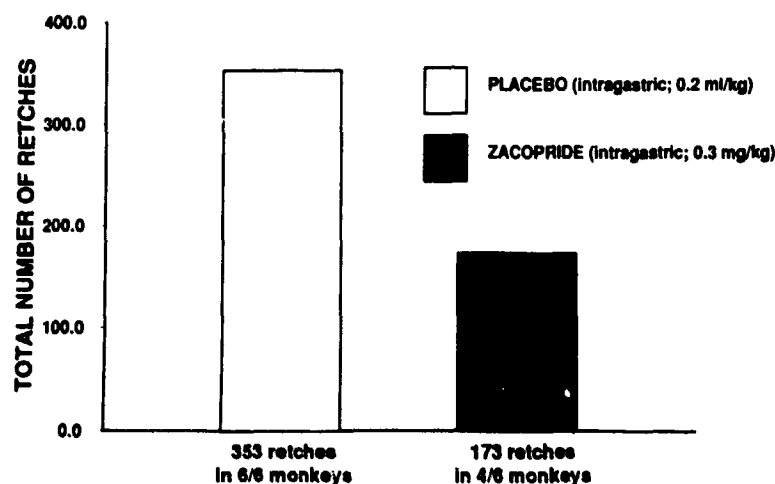
FIG. 4. Effect of zacopride on the number of radiation-induced retches. Placebo or zacopride was given intragastrically 30 min before irradiation, and the number of retches was determined using a videotape. Retching was defined as a nonproductive vomiting.

Following irradiation, 70 emeses were observed in 5 of 6 monkeys after placebo (the 6th monkey experiencing only retching, as described below), compared to only 1 emesis in 1 of 6 monkeys after zacopride (Fig. 2; $P < 0.01$). As illustrated by the time course of emesis following irradiation (Fig. 3), most vomiting occurred during the first hour after placebo, whereas the only vomiting after zacopride was seen at about 2 h. Similarly, 353 retches were observed in 6 of 6 monkeys after placebo compared to 173 retches in 4 of 6 monkeys after zacopride (Fig. 4; $P < 0.01$). In addition,
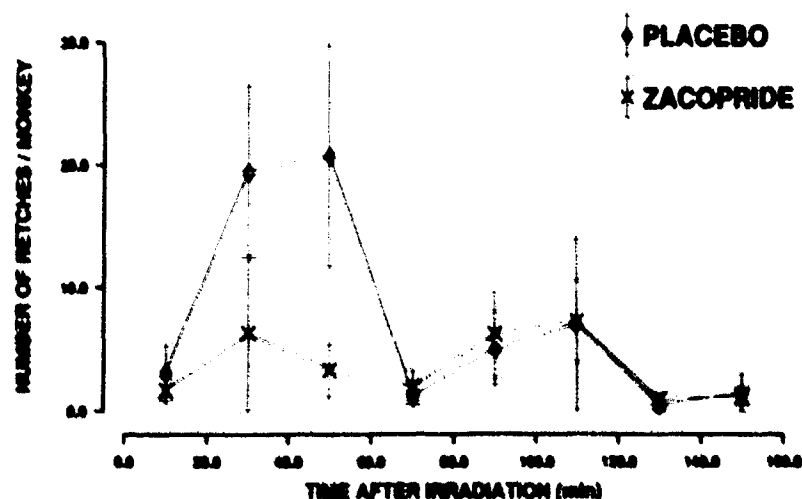

FIG. 5. Effect of zacopride on the time course of radiation-induced retching. Placebo or zacopride was given intragastrically 30 min before irradiation, and the number of retches determined using a videotape was averaged for each 20-min period. Retching was defined as nonproductive vomiting. Values are means ± SE.
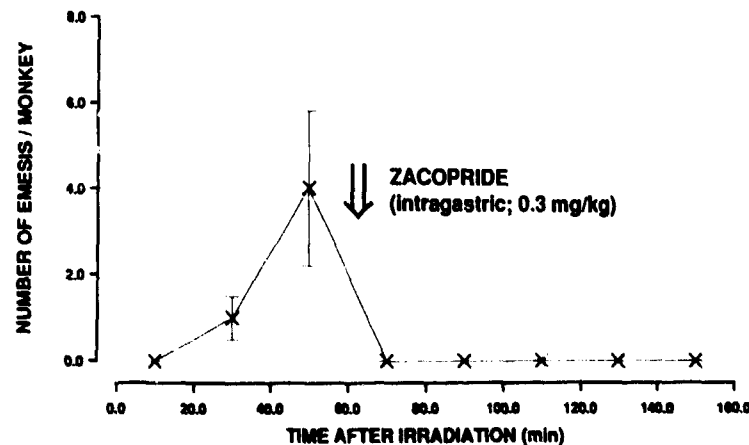
FIG. 6. Effect of zacopride administered after the first emesis on the time course of radiation-induced vomiting. Zacopride was given intragastrically after the first emesis had occurred (i.e., between 50 and 60 min after irradiation) and the number of emeses determined using a videotape was averaged for each 20-min period. Values are means ± SE.

most retching occurred during the first hour after placebo, and zacopride significantly reduced the number of retches during that period, but not during the second hour (Fig. 5). When compared to placebo given before irradiation, administration of zacopride to another group of irradiated monkeys after vomiting had started (i.e., about 30 min after irradiation) significantly inhibited the occurrence of retching and vomiting during the subsequent 100 min of observation (retches: 2 vs 84; emeses: 0 vs 25; $P < 0.05$). The time course of this effect is depicted graphically in Figs. 6 and 7.

Zacopride did not significantly modify fractional gastric emptying (FER) in the control state during fasting or after a water meal (Table I). After irradiation plus
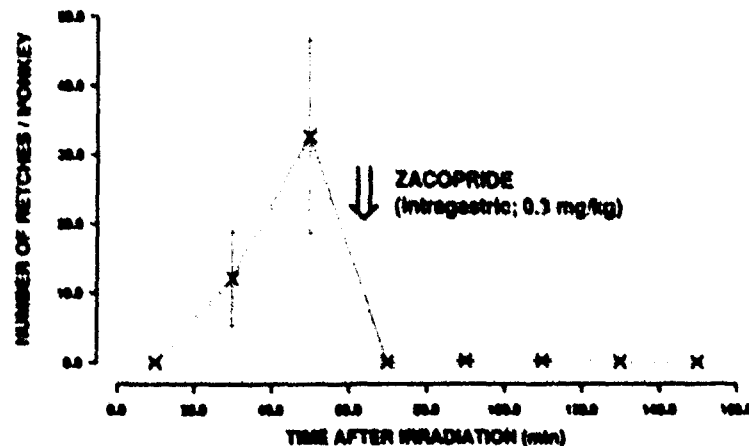

FIG. 7. Effect of zacopride administered after the first emesis on the time course of radiation-induced retching. Zacopride was given intragastrically after the first emesis had occurred (50–60 min after irradiation), and the number of retches determined using a videotape was averaged for each 20-min period. Values are means ± SE.

TABLE I

Effect of Zacopride, Radiation, and a Water Meal on Fractional Emptying Rate (in %/min)

	Control		Postirradiation	
	Fasting	*Postmeal*	*Fasting*	*Postmeal*
Placebo	3.42 ± 0.92	4.21 ± 0.64	$1.15 \pm 0.20^*$	$0.36 \pm 0.12^*$
Zacopride	4.66 ± 0.49	4.37 ± 0.69	$2.72 \pm 0.84^{*\dagger}$	$0.66 \pm 0.20^{*\dagger}$

Note. Values are $\pm$SE.

* $P < 0.05$ compared to control.

$\dagger$ $P < 0.05$ compared to placebo using ANOVA with repeated measures.

placebo, gastric emptying was significantly slowed during fasting and after a meal (Table I; $P < 0.05$), effects which were significantly inhibited by zacopride ($P < 0.05$). However, irradiation still produced significant suppression of both fasting and postmeal FER even after zacopride ($P < 0.05$).

DISCUSSION

In the present studies, we determined the emetic and gastroplegic effects of nonuniform γ irradiation, studied the efficacy of zacopride in the prevention and treatment of radiation-induced vomiting and gastric suppression, and evaluated the potential side effects of this medication in the rhesus monkey.

In the basal nonirradiated state, intragastric administration of zacopride did not induce vomiting, retching, or abnormal behavior. In addition, zacopride did not impair performance on a visual discrimination task, demonstrating that it was not behaviorally toxic for this task. This finding was recently confirmed using a murine motor performance task ((*15*) and unpublished observations). Determining if a new drug has behavioral toxicity is important because this side effect may be as limiting as the adverse effect (emesis) the drug is designed to treat, e.g., in an emergency radiation situation (*16*).

Following irradiation, we determined the precise time course of vomiting and retching as well as the alterations of gastric emptying. Retching and vomiting started about 30 min after irradiation, decreased markedly after 70 min, and disappeared after 120 min. The present 30-min delay differs markedly from previous observations of a delay of almost 1 h after irradiation with doses of 400–550 cGy (*2*) and of a delay of less than 5 min following a dose of 1200 cGy (*17*). Thus, the interval between irradiation and vomiting appears to be inversely proportional to the dose received. In contrast, both the emetic response and the gastric suppression were similar to those observed after total-body irradiation in the same animal model with midtissue doses to the torso and abdomen identical to those used in the present experiments (800 cGy) (*4*). This dose of 800 cGy was selected because it was twice the ED_{50} for vomiting as previously determined by others for monkeys (*2, 17*). However, due to the exposure system chosen for the present experiments, the head midtissue doses were 30% higher than in our previous studies (*4*), and the tibia and femur midtissue doses

were, respectively, 47% and 27% lower. Taken together, these data suggest that the abdomen and torso are the most important targets for the initiation of the prodromal syndrome.

In the monkey exposed to 800 cGy ^{60}Co, intragastric administration of zacopride 15 min before irradiation prevented radiation-induced vomiting. In addition, zacopride significantly inhibited retching, although the time course of retching appears to have been only minimally altered by zacopride (Fig. 5). Due to the small number of subjects, the difference did not reach a level of statistical significance, but it is probable that the effect shown on Fig. 5 was real. In addition, intragastric administration of zacopride after the first episode completely suppressed retching and vomiting for the subsequent 100 min. Since zacopride did not significantly modify radiation-induced retching and vomiting from 60 to 120 min after exposure, the duration of the anti-emetic effect of zacopride in the present model appears to be about 1 h. Similarly, zacopride inhibited the suppression of gastric emptying induced by irradiation during fasting and after the water meal. Thus, after irradiation plus zacopride, gastric empty-ing was decreased by only 40% during fasting and by 85% after the meal. Since the meal was given about 1 h after zacopride, it appears that the duration of the gastroki-netic effect of the drug, like that of its antiemetic effect, was approximately 1 h. Taken together, these observations suggest that the current formulation of zacopride should be administered twice: once before irradiation and once after exposure. Although the improvement of gastric emptying induced by zacopride using the present frequency and dose of administration is not complete, it markedly improves the possibility of oral rehydration after exposure to radiation. It is most remarkable that zacopride has an antiemetic effect even when given intragastrically after irradiation and that it can actually interrupt radiation-induced vomiting and retching.

The mechanism by which radiation causes emesis and gastric inhibition, as well as the mechanism by which zacopride prevents these effects, remains hypothetical. The central nervous system appears to play a pivotal role in radiation-induced prodromal symptoms, as suggested by the observed rise of plasma β-endorphin following irradia-tion (4). This rise is similar to the one observed after exposure to stress (18, 19), which is known to inhibit gastric function (20). Thus the rise of plasma β-endorphin may be responsible in part for radiation-induced vomiting and gastric inhibition, since this type of effect has been observed after exogenous administration of opioids (21). Irradiation could cause the release of β-endorphin or of another humoral mediator by initially activating the peripheral end of afferent nerves. A direct effect of irradia-tion on the brain appears unlikely for at least three reasons. First, shielding of the area postrema (chemoreceptor trigger zone) does not prevent radiation-induced vomiting (22). Second, increasing the dose delivered to the head by 50% in the present study does not modify significantly the symptoms (4). Third, ablation of the area postrema in cats does not prevent radiation-induced vomiting (23). Zacopride is a benzamide derivative with gastrokinetic properties which does not protect against emesis caused by apomorphine-induced activation of the dopamine receptors of the area postrema (24). However, intravenous (iv) or intracerebroventricular zacopride prevents emesis induced by either iv chemotherapy agent (25). Since zacopride is not a dopamine antagonist, it is not neuroleptic and does not cause extrapyramidal, cardiovascular, or autonomic nervous system side effects. Given these facts, it is probable that zacopride

prevents radiation-induced vomiting and retching by acting at a site different than the area postrema, either centrally or at the periphery, but the exact mechanism of action remains to be defined.

In conclusion, we observed that radiation-induced emesis was accompanied by suppression of gastric emptying in monkeys. In addition, intragastric administration of zacopride significantly inhibited radiation-induced retching, vomiting, and suppression of gastric emptying. Although zacopride does not appear to cause detectable adverse behavioral side effects, further studies are needed to confirm this perception. The present observations have important implications in the treatment of radiation sickness and it will be important to determine if they can be confirmed in clinical studies.

ACKNOWLEDGMENTS

RECEIVED: February 8, 1988; REVISED: April 12, 1988

REFERENCES

1. R. A. CONARD, Some effects of ionizing radiation on the physiology of the gastrointestinal tract: A Review. *Radiat. Res.* 5, 167-188 (1956).

2. G. R. MIDDLETON and R. W. YOUNG, Emesis in monkeys following exposure to ionizing radiation. *Aviat. Space Environ. Med.* 46, 170-172 (1975).

3. A. DUBOIS, J. P. JACOBUS, M. P. GRISSOM, R. ENG, and J. J. CONKLIN, Altered gastric emptying and prevention of radiation induced vomiting in dogs. *Gastroenterology* 86, 444-448 (1984).

4. E. D. DORVAL, G. P. MUELLER, R. R. ENG, A. DURAKOVIC, J. J. CONKLIN, and A. DUBOIS, Effect of ionizing radiation on gastric secretion and gastric motility in monkeys. *Gastroenterology* 89, 374-380 (1985).

5. J. R. LACKNER and A. GRAYBIEL, Etiological factors in space motion sickness. *Aviat. Space Environ. Med.* 54, 675-681 (1983).

6. A. DUBOIS, Aspects of radiation-induced gastrointestinal injury and radioprotection. *Pharmacol. Ther.* 39, 67-72 (1988).

7. K. SCHULTZE-DELRIEU, Metoclopramide. *Gastroenterology* 77, 768-779 (1979).

8. J. W. THORPE and R. W. YOUNG, Monkey performance after partial body irradiation. *Aerosp. Med.* 42, 503-507 (1971).

9. R. L. MONROY, R. R. SKELLY, P. TAYLOR, A. DUBOIS, R. A. DONAHUE, and T. J. MACVITTIE, Recovery from severe hematopoietic suppression using recombinant human granulocyte-macrophage colony stimulating factor. *Exp. Hematol.* 16, 344-348 (1988).

10. A. DUBOIS, G. H. NATELSON, P. VAN EERDEWEGH, and J. D. GARDNER, Gastric emptying and secretion in the rhesus monkey. *Am. J. Physiol.* 232, 186-192 (1977).

11. J. M. FINDLAY, R. J. PRESCOTT, and W. SIRCUS, Comparative evaluation of water recovery test and fluoroscopic screening in positioning a nasogastric tube during gastric secretory studies. *Br. Med. J.* 4, 458-461 (1972).

12. J. A. HILDES and D. L. DUNLOP, A Method for estimating the rates of gastric secretion and emptying. *Can. J. Med. Sci.* **29**, 83–89 (1951).

13. J. D. GEORGE, New clinical method for measuring the rate of gastric emptying: The double sampling test meal. *Gut* **9**, 237–242 (1968).

14. G. W. SNEDECOR and W. G. COCHRAN, *Statistical Methods*, 5th ed., pp. 87–98. Iowa State Univ. Press, Ames, Iowa, 1980.

15. V. BOGO, T. A. HILL, and R. W. YOUNG, Comparison of accelerod and rotarod sensitivity in detecting ethanol- and acrylamide-induced performance decrement in rats: Review of experimental considerations of rotating rod systems. *Neurotoxicology* **2**, 765–787 (1981).

16. V. BOGO, A. J. JACOBS, and J. F. WEISS, Behavioral toxicity and efficacy of WR2721 as a radioprotectant. *Radiat. Res.* **104**, 182–190 (1985).

17. J. L. MATTSON and M. G. YOCHMOWITZ, Radiation-induced emesis in monkeys. *Radiat. Res.* **82**, 191–199 (1980).

18. R. GUILLEMIN, T. VARGO, J. ROSSIER, S. MINICK, N. LING, C. RIVIER, W. VALE, and F. BLOOM, β-endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. *Science* **197**, 1367–1369 (1977).

19. J. ROSSIER, E. FRENCH, C. RIVIER, N. LING, R. GUILLEMIN, and F. BLOOM, Foot-shock induced stress increases β-endorphin in rat blood but not brain. *Nature* **270**, 618–620 (1977).

20. A. DUBOIS and B. H. NATELSON, Habituation of gastric function suppression in monkeys after repeated free-operant avoidance sessions. *Physiol. Psychol.* **6**, 524–528 (1978).

21. P. T. SHEA-DONOHUE, N. ADAMS, J. ARNOLD, and A. DUBOIS, Effects of met-enkephalin and naloxone on gastric emptying and secretion in rhesus monkeys. *Am. J. Physiol.* **245**, G196–G200 (1983).

22. H. I. CHINN and S. C. WANG, Locus of emetic action following irradiation. *Proc. Soc. Exp. Biol. Med.* **85**, 472–477 (1954).

23. H. L. BORISON, L. E. McCARTHY, E. B. DOUPLE, J. JOHNSON, and R. BORISON, Acute radiation-induced vomiting in area postrema-ablated cats. *Radiat. Res.* **109**, 430–439 (1987).

24. R. S. ALPHIN, W. L. SMITH, C. B. JACKSON, D. A. DROPPELMAN, and L. F. SANCILIO, Zacopride (AHR-11190B), a unique and potent gastrointestinal, prokinetic and antiemetic agent in laboratory animals. *Dig. Dis. Sci.* **31**(10), 482S (1988). [Abstract]

25. W. L. SMITH, E. M. CALLAHAM, and R. S. ALPHIN, The emetic activity of centrally administered cisplatin and its antagonism by zacopride. *J. Pharm. Pharmacol.* **40**, 142–143 (1988).