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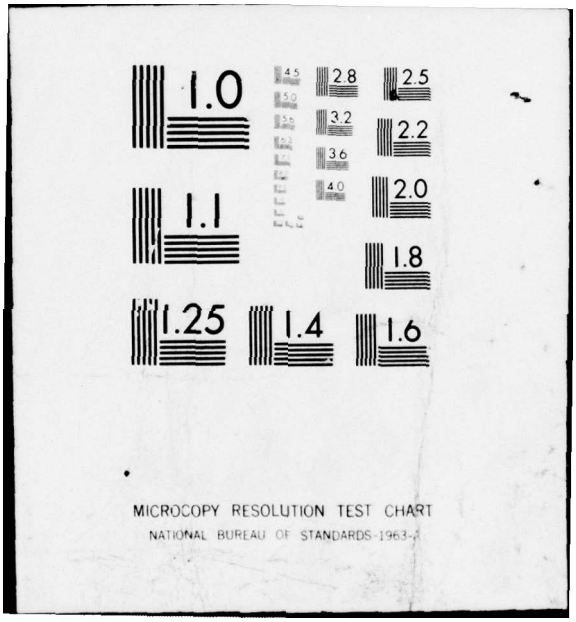
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DRUG INHIBITION OF FIRST-STAGE RADIOEMESIS

June 1977

Interim Report for Period 5 November 1975-31 December 1976

Approved for public release; distribution unlimited.

USAF SCHOOL OF AEROSPACE MEDICINE
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas 78235

NOTICES

This interim report was submitted by Mason Research Institute, Harvard Street, Worchester, Massachusetts 01608, under contract F41609-76-C-0014, job order 7757-05-31, with the USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas. Dr. Jerome H. Krupp (SAM/RZW) was the Laboratory Scientist-in-Charge.

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources--National Research Council.

This report has been reviewed by the Information Office (OI) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

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An animal model of irradiation-induced emesis was developed which involved exposing young male beagle dogs to 800 rads in the abdominal area. This caused a 100% incidence of emesis within 8 hr and a second wave of emesis and hemorrhagic diarrhea approximately 48 hr later. Seven drugs and one combination of two drugs were examined for effects against these responses. Chlorpromazine proved to be the most potent antagonist of first-stage emesis

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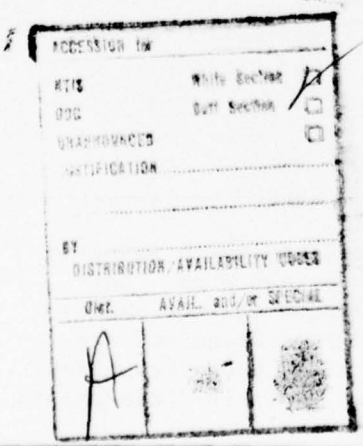
20. Abstract (Continued)

while dimenhydrinate and diphenhydramine HCl showed the same activity but to a lesser degree. Inactive drugs were phenytoin sodium, perphenazine (at a low dose), WR2721, and the combination of amphetamine plus scopolamine. Acetylsalicylic acid intensified the emetic responses.



DRUG INHIBITION OF FIRST-STAGE RADIOEMESIS

INTRODUCTION

Emesis following high-intensity irradiation is a well-established phenomenon which creates several medical problems. Cancer victims undergoing radiotherapy involving the abdominal viscera must endure this side effect of treatment (16). The same type of response could potentially inhibit the performance of individuals who are expected to carry out important tasks in the event of nuclear catastrophes, e.g., trained workers involved in nuclear power plant accidents, or military personnel during a thermonuclear war. Because of real and potential problems associated with radioemesis, a drug that reliably counteracts this effect would be a useful addition to the world's pharmacopoeia.

The emetic reactions which follow irradiation can be classified as either first or second stage, according to the time lapse between irradiation and emesis. As defined in dog studies, the first-stage emesis usually occurs within 6 hr after exposure; a second-stage emesis follows in 24 to 48 hr (25). The latter is accompanied by a severe hemorrhagic diarrhea. The irradiation dose producing these effects has been variously reported to be between 600 to 1200 rads for dogs (4, 12, 16, 25) and monkeys (5, 10). Based upon this information, a canine animal model for radioemesis was first designed and tested, and then employed to examine a number of selected drugs known either to have antiemetic activity, or to be capable of blocking a mechanism theoretically involved in radioemesis.

METHODS

Subjects

Male beagle dogs, weighing from 2.8 to 5.2 kg (average 4.5 kg), which were purchased from Beagles for Research Inc., North Rose, N.Y., were certified as immunized against distemper, hepatitis, and leptospirosis and free of heartworm. After acceptance, they were quarantined for 14 days, and the absence of enteric and exoparasites was established. Diet during the quarantine and experimental periods consisted of dry dog food (Wayne Feed Co., Chicago, Ill.) offered once daily. Water was automatically provided ad libitum. Food was withheld from 1600 of the previous day until 0900 of the day of exposure. Food was again offered 1 hr postirradiation and daily thereafter.

Each dog was weighed and a body temperature was taken weekly during quarantine, and daily following irradiation. Cage-side observations were recorded: daily, during quarantine; continuously, until the first emetic

episode following irradiation; hourly, for the next 12 hr; and thrice daily, for 7 days thereafter. These observations included food and water intake, signs of emesis, indications of diarrhea or abnormal urine, and the animal's general appearance. On the eighth day, surviving dogs were euthanized and necropsied. All internal organs were examined in situ and, following dissection, the intestinal tract was opened and the mucosa inspected. Specimens from five levels of the gut were removed and stored in formalin.

Anesthesia

Light surgical anesthesia was induced and maintained to effect by giving methoxyflurane (Metofane) through a rubber face mask, from a Heidbrink Kinet-o-meter gas anesthesia machine (Ohio Chem. Mfg. Co., Madison, Wis.). No preanesthetic was used. In a pilot experiment, this regimen did not cause emesis in three dogs which were anesthetized and allowed to recover, without irradiation. Breathing was monitored during anesthesia as a precaution against respiratory arrest. A Harvard movement transducer and a pressure sensitive transducer were attached to the abdominal muscles and thoracic wall, respectively. The combination of movement generated by inspiration/expiration and pressure created by the heartbeat produced a signal which was transmitted first into a low-level DC preamplifier, then to a polygraph DC amplifier (Grass Instruments Co., Quincy, Mass.), and finally to a dual-beam oscilloscope (Model 502A, Tektronix Inc., Portland, Ore.) for visual observation.

Restraint in a fixed lateral recumbent position was by a plaster body cast with an opening over the lateral abdominal wall to admit a 10 cm x 10 cm irradiation cone, a field covering the area between the xiphoid and cranial edge of the pubis.

Irradiation

The radio delivery unit (a Picker Model 736) operated at 200 kV, 25 ma and 0.25 mm Cu filtration and produced a beam with a half-value thickness of 1.1 mm Cu at an output in air of approximately 50 R/min. Exposure time, adjusted for differences in abdominal width, ranged from 16 to 20 min. Each animal was laterally exposed to each side for one-half the total exposure time. This technique produced a calculated dose of 800 rads, at 1/2 cm depth, uniformly distributed throughout the abdominal area.

Drug Treatment

Except for WR2721, all drugs were purchased from commercial sources as clinical formulations (Table 1). Dose levels for all standard drugs were selected from a textbook, Current Veterinary Therapeutics (14), or the published results of a comprehensive study of antiemetics in dogs (28). A canine dose for WR2721 was extrapolated from the dose which was reported to be radioprotective in mice (23) by using the interspecies conversion factors of Freireich (11). If no specific antiemetic dose

TABLE 1. DRUGS, DOSE, AND MANUFACTURERS

Drug name		Total daily dose	Dose schedule		Manufacturer
Generic	Common		Day 1	Day 2-7	
Acetylsalicylic acid (ASA)	*Aspirin*	2 g	1 g @ -60, -30 min	1 g, b.i.d.	United Research Laboratories, Phila., Pa.
Amphetamine + scopolamine	Benzedrine + hyoscine	10 mg + 0.6 mg	10 mg + 0.6 mg + @ -15 min	10 mg + 0.6 mg, b.i.d.	Eli Lilly Co., Indianapolis, Ind.
Chlorpromazine	Thorazine	50 mg	25 mg @ -60, -30 min	25 mg, b.i.d.	Smith, Kline and French Laboratories, Phila., Pa.
Dimenhydrinate	Dramamine	50 mg	50 mg @ -30 min	25 mg, b.i.d.	Searle Laboratories, Chicago, Ill.
Diphenhydramine HCl	Benadryl	25 mg	12.5 mg @ -60, -30 min	12.5 mg, b.i.d.	Parke-Davis, Detroit, Mich.
Oxytetracycline HCl	Terramycin	0.5 g	250 mg @ -60, -30 min	250 mg, b.i.d.	Pfizer Laboratories, New York, N.Y.
Perphenazine	Trilafon	4 mg	4 mg @ -30 min (5 dogs) 4 mg @ -60 min (8 dogs)	2 mg, b.i.d.	Schering Corp., Kenilworth, N.J.
Phenytoin Na	Dilantin	60 mg	30 mg @ -60, -30 min	30 mg, b.i.d.	Parke-Davis, Detroit, Mich.
S-2-(3-Amino propylamino) ethyl phosphorotioic acid	WR2721		75 mg/kg	None	Walter Reed Institute of Research, Washington, D.C.

was available, then doses recommended for other therapeutic purposes were used with the highest dose selected whenever a range of doses was suggested. Drugs were administered as the clinical formulation except WR2721 which was weighed according to individual dog requirements and packed in gelatin capsules for oral administration. Generally each dog was treated with half the total dose at 1.0 and 0.5 hr before irradiation, and the same daily dose was continued following exposure for an additional 6 days to investigate the possibility of effects on second-stage responses.

Analysis

Intergroup comparisons of first-stage onset time, duration, and number of episodes were accomplished by the Kruskal-Wallis test with $\alpha = .05$. Dunn's (9) multiple comparison procedure using Kruskal-Wallis rank sums was used to detect significant differences. When an animal did not vomit, his onset and duration times were respectively set equal to 999 and 0 min. The advantage of using Kruskal-Wallis rank sums was that it permitted inclusion of animals that did not vomit in determining the efficacy of each drug. This could not have been possible with parametric multiple comparison techniques. The choice of $\alpha = .05$ made this test conservative in the number of significant differences it could detect. The need to find the best drug or group of drugs was our rationale for employing this conservative procedure. Appendix A summarizes the raw onset, episode, and duration date for those wishing to consider more liberal testing procedures.

A comparison of weight by treatment group for the first 4 days was accomplished by Page's (19) distribution free test based upon Friedman rank sums. These findings indicate on which days weights were significantly different ($\alpha = .05$) by the multiple comparison procedure given in Hollander and Wolfe (13, page 151, eq. 15). A comparison of relative body weight change was also accomplished comparing percent weight changes on days 2, 3, and 4 with day 1 (cf. Hollander and Wolfe (13), page 155, eq. 20). Appendix B summarizes the raw weights during the first 4 days of this experiment.

RESULTS

Individual Group Responses

Controls--Thirteen dogs were irradiated, but not treated, and provided a representative pattern of postirradiation response. All control dogs recovered from the anesthesia and were able to stand unassisted within 5 min after irradiation. Each dog then had at least three emetic episodes with a group mean of 6.6 per dog, ranging from 3 to 10. A single dog vomited 5 min postirradiation; the remainder began vomiting after 20 to 90 min. The group average for time of onset was 46 min. The duration of emesis, or the time between the first and last episode, averaged 118 min. Table 2 summarizes first-stage emesis data for all animals including a statistical analysis by treatment group.

TABLE 2. SUMMARY AND STATISTICAL ANALYSIS OF FIRST-STAGE EMESIS

Drug	First-stage emetic incidence	First-stage emesis ($\bar{X} \pm$ S.D.)[a]			Mortality
		No. episodes	Onset time (minutes)	Duration (minutes)	
Control	13/13	6.62 ± 2.57	45.77 ± 23.08	118.08 ± 50.64	5/13
Acetylsalicylic Acid (ASA)	12/12	9.0 ± 2.52	27.08 ± 10.97	157.08 ± 55.66	4/12
Amphetamine + scopolamine	13/13	5.31 ± 2.02	45.38 ± 19.31	113.08 ± 40.34	0/13
Chlorpromazine	6/13	2.83 ± 1.94[b]	111.67 ± 37.51[b]	55.83 ± 38.39[b]	0/13
Dimenhydrinate	10/12	3.10 ± 1.79[b]	90.00 ± 21.86[b]	83.50 ± 38.66	4/12
Diphenhydramine HCl	13/13	3.77 ± 1.74[b]	92.31 ± 33.20[b]	61.15 ± 27.63[b]	2/13
Oxytetracycline HCl	3/3	4.33 ± 2.08	70.00 ± 10.00	73.33 ± 27.54	0/3
Perphenazine	12/12	5.17 ± 1.85	64.17 ± 16.49	90.83 ± 12.03	1/13
Phenytoin Na	11/12	6.36 ± 2.80	72.27 ± 40.58	82.27 ± 33.79	0/12
WR2721	7/7	7.14 ± 3.44	43.57 ± 17.01	98.57 ± 43.66	0/7

[a]The means and standard deviations were computed only for animals that had emetic episodes in order to permit a quantitative description of the prodromal syndrome.

[b]In comparing emetic responders only, these groups were found to be statistically different from control vs. treatments comparison (Hollander & Wolfe (13), p. 131, eq. 25) at the 5 percent level of significance.

Second-stage responses consisting of anorexia, emesis, and diarrhea began at a low incidence on the second day and reached a maximum incidence on day 5 for anorexia and day 4 for emesis and diarrhea. These symptoms were accompanied by a weight loss which depressed weights below the starting level by day 4. Undoubtedly, the anorexia and diarrhea contributed to this response. On day 5, a lethal effect at this dosage was demonstrated when 5 of the 13 dogs died. Gross lesions were found only in dogs which died and consisted of vascular injection and distended segments of the small and large intestine which contained a muco-hemorrhagic fluid. The remaining dogs, at necropsy on day 8, had grossly normal intestines, despite postirradiation diarrhea. Second-stage response data for all animals are shown in Table 3.

Dimenhydrinate--Treatment with this drug at 50 mg/dog/day produced a decrease in both total number and incidence of first-stage emetic episodes in the treated group compared with the control dogs, with a complete absence in 2 treated dogs. The onset of vomiting was delayed, but the duration of the emetic period was not shortened. Second-stage effects were seen as a higher incidence of emesis and diarrhea during the postirradiation period. Body weight loss and the pattern of gross lesions were similar to control dogs. Surviving dogs showed no changes while dogs which died had intestinal lesions consisting of fluid distention, vasculature congestion, and a flattened, ulcerated mucosa. One dog had an additional lesion, an enteric intussusception, which was presumed to be the major cause of death.

Acetylsalicylic Acid (ASA)--A dose of 2 gm/dog/day of aspirin had an adverse effect by increasing the number of first-stage emetic episodes to an average of 9.0 for this group. The mean response began 19 min earlier than in controls and lasted an average of 39 min longer. Second-stage emesis appeared in all dogs on day 2, but in only 3 of 13 control dogs on day 2. Four of 12 dogs died, a mortality rate (33.3%) consistent with control dogs. The gross pathological picture was the same as controls, e.g., congestion and fluid distention in dogs which died plus a single case of intussusception. Surviving dogs were grossly normal.

WR2721--Seven dogs were irradiated and treated with this experimental radioprotective compound. First-stage emesis was unaffected by a dose of 75 mg/kg. The period of second-stage emesis was shortened and ended sooner than in the controls.

Chlorpromazine--This tranquilizer proved to be the most effective in inhibiting first-stage emesis, with no episodes in 7 of 13 dogs. In those animals which did respond, the mean onset time was significantly delayed ($\alpha = .05$). Using liberal hypothesis testing procedures (cf. Table 2) the mean number of episodes, 2.8, and the duration of emesis in responders were also significantly reduced. The incidence of anorexia was reduced during the 7 days following irradiation. No alterations were produced in the pattern of second-stage emesis and diarrhea. All 13 dogs survived the 8-day observation period and showed no gross lesions at necropsy.

TABLE 3. THE EFFECT OF ANTIEMETICS ON THE INCIDENCE OF SECOND-STAGE RESPONSES IN IRRADIATED BEAGLE DOGS

Drug	Day of study																								
	Anorexia							Emesis							Diarrhea										
	2	3	4	5	6	7	8	2	3	4	5	6	7	8	2	3	4	5	6	7	8				
Control	1/13	6/13	9/13	6/8	3/8	3/8	1/8	3/13	10/13	11/13	2/8	1/8	0/8	0/8	4/13	10/13	13/13	6/8	5/8	4/8	0/8				
Acetylsalicylic acid (ASA)	0/12	4/12	9/12	11/12	10/12	7/8	0/8	12/12	11/12	12/12	10/12	3/12	2/8	0/8	5/12	9/12	11/12	8/12	9/12	5/8	1/8				
Amphetamine + scopolamine	0/13	3/13	5/13	0/13	2/13	1/13	0/12	5/13	10/13	4/13	3/13	1/13	0/13	0/12	0/13	2/13	11/13	12/13	13/13	6/13	1/12				
Chlorpromazine	0/13	1/13	2/13	0/13	0/13	0/13	0/13	2/13	11/13	6/13	0/13	0/13	0/13	0/13	0/13	11/13	11/13	6/13	6/13	3/13	2/13				
Dimenhydrinate	0/12	1/12	12/12	8/10	3/9	0/9	0/8	9/12	10/12	9/12	3/10	3/9	0/9	0/9	2/12	10/12	12/12	8/10	8/9	5/9	3/9				
Diphenhydramine HCl	10/13	5/13	6/12	6/11	1/11	0/11	0/11	5/13	6/13	0/12	1/11	0/11	0/11	0/11	4/13	10/13	12/12	11/11	9/11	5/11	1/11				
Oxytetracycline HCl	0/3	1/3	2/3	2/3	0/3	0/3	0/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	3/3	3/3	2/3	1/3	0/3				
Perphenazine	0/13	5/13	9/13	4/12	1/12	1/12	0/12	2/13	13/13	6/13	0/12	0/12	0/12	0/12	0/13	9/13	11/13	10/12	8/12	0/12	1/12				
Phenytoin Na	0/12	3/12	5/12	1/12	0/12	0/12	0/12	2/12	10/12	5/12	1/12	0/12	0/12	0/12	2/12	10/12	10/12	10/12	8/12	4/12	0/12				
WR2721	1/7	0/7	2/7	1/7	0/7	0/7	0/7	0/7	2/7	5/7	0/7	0/7	0/7	0/7	4/7	3/7	5/7	7/7	5/7	4/7	2/7				

Phenytoin sodium--This drug produced no clinical changes which might distinguish treated animals from controls. All dogs survived for 8 days and showed no gross lesions at necropsy.

Diphenhydramine HCl--This antihistamine showed activity against first-stage emesis in that the onset of emesis was delayed to twice that of controls, e.g., 45.8 vs 92.3 min. The incidence of second-stage emesis also appeared to be reduced, as 5 treated dogs were completely free of this response. All control dogs vomited on at least one day during the week following irradiation. In addition, in the other 5 dogs in the diphenhydramine group, second-stage emesis occurred only once. In the control group, only 1 dog showed this same limited response. One chlorpromazine-treated dog was free of second-stage emesis, another 5 vomited on only one day, and 7 vomited on two successive days. Moreover, in the diphenhydramine-treated group, second-stage emesis was restricted to the first 72 hr postirradiation, except for a single dog which vomited once on day 5. Severe diarrhea occurred during the postirradiation period and caused the death of 2 dogs which showed typical gross lesions at necropsy, i.e., congested splanchnic vessels and intestinal loops distended by a red-brown liquid. The mucosa appeared to be flattened. Survivors were grossly normal.

Perphenazine--This tranquilizer was administered at a low dose (4 mg/dog) and caused a moderate, though insignificant, depression in episodes of first-stage emesis with a delayed onset. Otherwise, the only change during the week following irradiation was a significant loss of body weight. One dog died and showed an intussusception with vascular congestion and distended intestines at necropsy. Survivors were grossly normal.

Amphetamine + Scopolamine--This combination had no positive effect on first- or second-stage responses which would distinguish the treated group from controls. One dog was euthanized in extremis on the eighth day following irradiation. Gross lesions in this animal were a necrotizing jejuno-ileal intussusception with congestion and fluid distention of the intestines. Survivors showed no gross lesions at necropsy.

Oxytetracycline HCl--Because of the small sample (3 dogs), no definite conclusions can be made regarding the effect of this antibiotic. Noteworthy was an apparent reduction in the number of second-stage emetic responses and the delay in onset of diarrhea (Table 3). All 3 dogs survived, and gross lesions were absent at necropsy.

Comparative Intergroup Responses

Intergroup comparisons of first-stage onset time, duration, and number of episodes led to the following significant differences at the 0.05 level.

Number of Emetic Episodes in All Subjects--

Chlorpromazine, Dimenhydrinate < Control, ASA[1]
Chlorpromazine < WR2721, Phenytoin Na

Emetic Onset Times in All Subjects--

Chlorpromazine, Dimenhydrinate > Control
Chlorpromazine, Dimenhydrinate, Diphenhydramine HCl > ASA

Duration Time in All Subjects--

Chlorpromazine < Control
Chlorpromazine, Diphenhydramine HCl, Dimenhydrinate < ASA

Chlorpromazine and dimenhydrinate significantly reduced the number of episodes and prolonged onset times compared to controls. Only chlorpromazine dogs had shortened duration times when compared to the control group. Chlorpromazine was also more effective in minimizing episodes compared with WR2721 and phenytoin Na. If one were to apply the more liberal procedure of testing all treatments vs. the control (Hollander & Wolfe (13), p. 131), one would additionally conclude that diphenhydramine HCl significantly (α = .05) diminished the number of emetic episodes, delayed onset times, and minimized duration times compared to the control group.

Since treatment groups can be divided into responders and nonresponders. we also asked which treatments minimized effects in responders by applying multiple comparison procedures. At the α = .05 level we found the following:

Number of Episodes in Emetic Responders--

Chlorpromazine, Dimenhydrinate, Diphenhydramine HCl < ASA

Onset Time in Emetic Responders--

Chlorpromazine, Dimenhydrinate, Diphenhydramine HCl > Control, ASA
Chlorpromazine > WR2721, Amphetamine + Scopolamine
Phenytoin Na > ASA

Duration Time in Emetic Responders--

Diphenhydramine HCl < ASA

---

[1]When two or more items on the same line are separated by commas, no differences were detected. Inequalities "<" and ">" represent "less than" and "greater than" at the 0.05 level.

Thus, chlorpromazine, dimenhydrinate, and diphenhydramine HCl most effectively delayed onset times. In addition, they exceeded ASA in minimizing the number of emetic episodes among responders. Finally, phenytoin Na delayed emetic onset better than ASA and showed more effectiveness in minimizing the emetic vulnerability period. Applying the more liberal procedure of testing all treatments vs. a control ($\alpha = .05$) one would additionally conclude that chlorpromazine, dimenhydrinate, and diphenhydramine HCl minimized the number of episodes in emetic responders and chlorpromazine shortened duration time.

Body Weight Changes

Table 4 summarizes by group the mean and standard deviations of individual body weights expressed as a percentage of weight on day 1. No statistically significant weight losses could be detected in the WR2721 and chlorpromazine groups during the first 4 days. Amphetamine + scopolamine and diphenhydramine HCl exhibited statistically significant weight loss on day 2. The remaining groups had weight losses which could be detected beginning day 3. Table 5 summarizes by group all interday comparisons as opposed to comparisons with day 1 only in Table 4.

DISCUSSION

Vomiting is a complicated physiological act which involves, among other things, smooth muscle relaxation in the stomach and esophagus concurrent with contraction of skeletal muscle in the diaphragm, thorax, and abdominal wall. This series of events is centrally initiated and coordinated by two paired control centers located beneath the floor of the fourth ventricle, the chemoreceptor trigger zone (CTZ) which lies in the lateral segment of the area postrema and the vomiting center found near the fasciculus solitarius and the adjacent reticular formation (6). Besides being anatomically separated, each is distinguished by receptivity to either chemical or sensory stimuli. The CTZ responds directly to blood-borne substances, such as apomorphine, while the vomiting center receives neural impulses via the sympathetic and parasympathetic pathways from locations such as the gastrointestinal tract, vestibular apparatus, and presumably the CTZ. Evidence for the existence of these functionally separate control centers comes from classical experiments whereby apomorphine was shown to induce voming in intact dogs and dogs which were previously sympathectomized and vagotomized, but not in dogs with ablated CTZs. Conversely, copper sulfate is emetic in intact dogs or dogs lacking functional CTZs, but not in dogs with interrupted parasympathetic and sympathetic pathways from the abdominal mucosa, unless massive doses are given (24). The results of these and corroborating experiments are generally accepted as indicating that apomorphine acts directly on the CTZ while $CuSO_4$ at low doses stimulated peripheral nerve receptors in the intestinal tract

TABLE 4. RELATIVE BODY WEIGHT CHANGES[a] IN IRRADIATED DOGS

Drug	Dog No.	Day of study $\bar{X} \pm S$			
		1	2	3	4
Control	13	1.0	.97 ± .04	.94 ± .05	.85 ± .06[b]
Amphetamine + scopolamine	13	1.0	.94 ± .02[b]	.95 ± .02[b]	.89 ± .03[b]
Acetylsalicylic acid (ASA)	12	1.0	.97 ± .04	.92 ± .04	.85 ± .04[b]
Chlorpromazine	13	1.0	1.01 ± .01	.97 ± .02	.92 ± .04
Dimenhydrinate	12	1.0	.98 ± .03	.96 ± .03[b]	.88 ± .03[b]
Diphenhydramine HCl	13	1.0	.97 ± .01[b]	.94 ± .03[b]	.90 ± .07[b]
Perphenazine	13	1.0	.99 ± .02	.96 ± .02[b]	.89 ± .03[b]
Phenytoin Na	12	1.0	.99 ± .01	.97 ± .02[b]	.90 ± .04[b]
WR2721	7	1.0	.96 ± .02	.94 ± .02	.90 ± .03

[a]Expressed as a percent of preirradiation (day 1) body weight.

[b]Significantly ($\alpha = 0.05$) less than day 1 using multiple comparison procedures found in Hollander and Wolfe (13, p. 155; eq. 20). Differences in chlorpromazine relative body weights between days 1 and 4 could not be detected because they depend on rankings from the intervening days. This also applies to ASA (day 1 vs. day 3) and WR2721 day 1 vs. day 4.

TABLE 5. DAILY BODY WEIGHT TRENDS[a]

Drug	Significant weight trend loss (at $\alpha = .05$) using Page's test	Comparative daily observation using Hollander & Wolfe (13, p. 151, eq. 15)
Control	Yes	1,2>4
Amphetamine + scopolamine	Yes	1>3, 4 and 2>4
Acetylsalicylic acid (ASA)	Yes	1,2,3>4
Chlorpromazine	No	
Dimenhydrinate	Yes	1>3,4 and 2>4
Diphenhydramine HCl	Yes	1>3,4 and 2>4
Perphenazine	Yes	1,2>4
Phenytoin Na	Yes	1>3,4 and 2>4
WR2721	No	

[a]Detailed analysis for days 5-8 was not done because of confounding effect of animal deaths within various treatment groups.

which transmit impulses directly to the vomiting center. High oral doses of the latter may be absorbed and directly stimulate the emetic center.

The genesis of first- or second-stage radioemesis is incompletely understood at this time. The available experimental results can be explained by hypothesizing that an unknown humoral substance(s) is absorbed from the irradiation-damaged intestine or the lining epithelium, which stimulates the CTZ. The destructiveness of irradiation to the small intestine is well established (3), and the present study confirms that an 800-rad exposure restricted to the abdomen will initiate early and late stages of vomiting. Moreover, studies in dogs (4, 7, 25) and monkeys (5) have shown that destroying the CTZ in the area postrema leads to an inhibition of the first- (but not second) stage emesis, while complete visceral denervation, by cutting the vagi and removing sympathetic chains, is ineffective. Pretreatment with chlorpromazine protects dogs against apomorphine-induced emesis (26) and radioemesis as shown in this study and elsewhere (8). Further supportive evidence for the existence of an enteric-CTZ pathway which responds to a cytotoxic stimulus comes from studies of nitrogen-mustard-induced emesis. This alkylating radiomimetic agent causes gastrointestinal damage and emesis in intact dogs. The latter response is absent in CTZ-ablated dogs (2).

An important organ in stimulating the vomiting reflex during motion sickness is the vestibular apparatus. In this example, the stimulus originates in the vestibule or semicircular canal and follows neural pathways to reach the vomiting center and/or the CTZ. From a pharmacological viewpoint, this mechanism is important because it demonstrates that cholinergic transmission is involved in emesis induction. In cats, intravenous physostigmine causes a marked increase in the firing rate of the vestibular neurons. This effect is antagonized by atropine, scopolamine, dimenhydrinate, and diphenhydramine HCl (15). Moreover, the same anticholinergic drugs depress the spontaneous firing activity of vestibular neurons in untreated cats. Consistent with these findings are the reports of anticholinergic effectiveness in combating motion sickness (27). The absence of CTZ depression by these drugs was shown in the study of Schmidt et al. (22) in which neither dimenhydrinate nor diphenhydramine HCl given at antiemetic doses inhibited apomorphine- or $CuSO_4$-induced emesis. Both of these anticholinergic/antihistaminic drugs significantly suppressed first-stage radioemesis in our studies. The exact mechanism is uncertain since a combination of anticholinergic and sympathomimetic drugs, scopolamine and amphetamine, was ineffective. Perhaps the antihistamine component of dimenhydrinate or diphenhydramine HCl is the more important since histamine, a known emetic agent (21), may be absorbed from the gut or released systemically from irradiated intestinal cells, and the use of antihistamines in treating irradiation sickness has been reported (17).

Assuming that the intestinal mucosa might be the source of radioemetic stimuli, other drugs were included which might inhibit biogenic pathways involved in causing radioemesis. Mice irradiated with 500 or 750 rads had increased levels of hepatic and cerebral prostaglandin E_1,

presumably because of an increased synthesis (20). The possibility that these substances are involved in causing irradiation side effects was further suggested by a report that acetylsalicylate in a buffered formulation reduced bowel motion and relieved abdominal pain and flatulence in cancer patients receiving radiotherapy (18). These beneficial effects were attributed to the known antiprostaglandin properties of aspirin. In the present study, aspirin was ineffective in blocking first- or second-stage radioemesis.

The effect of administering a thiophosphate radioprotective agent, WR2721, was examined with the view that perhaps protecting the epithelial mucosa might interrupt a chain of events which initiate radioemesis. WR2721 was considered a suitable candidate to test this hypothesis since it was shown to protect the intestinal mucosa in mice (23). This compound protected dogs against postirradiation weight loss; otherwise it failed to show useful activity.

Oxytetracycline HCl was selected for study as a broad spectrum antibacterial drug because of several indications that the gut flora, or their toxins, might play a role in irradiation emesis (1, 12). Our study was inconclusive because of the small sample size.

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APPENDIX A

EPISODE, ONSET, DURATION SUMMARY

Dog No.	Episodes	Onset (min)	Duration (min)
Control Dogs (Irradiated, nontreated)			
14-1	8	60	180
14-2	5	90	90
14-3	5	60	90
14-4	3	45	80
14-5	9	5	190
14-6	10	45	190
14-7	9	30	60
14-8	7	30	100
14-12	3	80	40
14-20	5	40	110
14-27	4	20	130
14-35	10	45	175
14-42	8	45	100
Amphetamine, 10 mg/dog & scopolamine, 0.6 mg/dog			
14-103	6	25	195
14-104	7	65	95
14-105	8	50	115
14-106	3	40	120
14-107	5	45	75
14-108	5	30	200
14-109	3	40	90
14-110	2	20	115
14-111	6	30	70
14-112	5	85	90
14-113	6	75	100
14-114	4	45	95
14-115	9	40	110
Dimenhydrinate, 50 mg/dog			
14-9	1	125	30
14-10	0	999	0
14-11	4	100	60
14-13	2	75	65
14-14	3	75	55
14-15	2	105	45
14-16	5	80	100
14-17	2	120	150
14-18	7	70	120
14-19	0	999	0
14-21	3	90	120
14-22	2	60	90
Phenytoin Na, 60 mg/dog			
14-63	9	60	125
14-64	5	100	75
14-66	12	70	70
14-67	6	35	135
14-68	6	5	50
14-69	6	80	85
14-70	6	55	105
14-71	8	75	105
14-72	7	50	85
14-73	4	105	40
14-74	1	160	30
14-75	0	999	0

Dog No.	Episodes	Onset (min)	Duration (min)
ASA, 2 g/dog			
14-24	9	25	150
14-25	8	50	165
14-26	9	15	70
14-28	5	40	90
14-30	6	25	130
14-31	9	15	180
14-32	14	20	120
14-33	13	30	160
14-34	6	20	120
14-36	9	40	225
14-37	8	25	250
14-38	10	20	225
Chlorpromazine, 50 mg/dog			
14-50	0	999	0
14-51	0	999	0
14-52	2	120	25
14-53	0	999	0
14-54	1	180	30
14-55	0	999	0
14-56	1	70	30
14-57	4	110	45
14-58	0	999	0
14-59	6	95	85
14-60	3	95	120
14-61	0	999	0
14-62	0	999	0
Diphenhydramine HCl, 25 mg/dog			
14-76	3	120	55
14-77	2	110	30
14-78	2	110	60
14-79	4	115	50
14-80	1	150	30
14-82	5	75	90
14-83	6	75	70
14-84	6	45	90
14-85	4	70	75
14-86	5	45	110
14-87	3	75	35
14-88	6	75	80
14-89	2	135	20
Perphenazine (4 mg/dog)			
14-90	6	80	85
14-91	8	60	80
14-92	5	55	75
14-93	3	55	110
14-94	3	70	80
14-95	3	45	95
14-96	4	40	95
14-97	7	80	85
14-98	6	50	95
14-99	5	90	115
14-100	8	85	90
14-101	0	999	0
14-102	4	60	85

APPENDIX B

POSTIRRADIATION BODY WEIGHT (kg) CHANGES

Dog No.	Day of study 1	2	3	4
Control dogs (irradiated, nontreated)				
14-1	4.7	4.5	4.7	4.5
14-2	4.7	4.6	4.6	4.1
14-3	4.8	4.7	4.5	4.15
14-4	4.6	4.8	4.6	4.2
14-5	4.35	3.95	3.75	3.28
14-6	4.9	4.55	4.15	3.8
14-7	4.25	3.9	3.8	3.32
14-8	4.3	4.0	3.9	3.42
14-12	4.95	4.8	4.75	4.35
14-20	4.75	4.6	4.55	3.90
14-27	4.2	4.25	4.1	3.85
14-35	4.25	4.15	4.1	3.85
14-42	4.1	4.15	4.0	3.6
Amphetamine, 10 mg/dog & scopolamine, 0.6 mg/dog				
14-103	4.8	4.7	4.6	4.2
14-104	5.2	5.0	5.0	4.8
14-105	5.0	4.8	4.6	4.2
14-106	5.0	5.1	4.9	4.8
14-107	4.6	4.5	4.5	4.1
14-108	4.7	4.7	4.4	4.1
14-109	4.7	4.6	4.5	4.2
14-110	5.0	4.7	4.7	4.5
14-111	4.9	4.8	4.8	4.4
14-112	4.7	4.5	4.4	4.0
14-113	4.4	4.2	4.2	3.9
14-114	4.9	4.7	4.7	4.5
14-115	4.8	4.5	4.3	4.0
Dimenhydrinate, 50 mg/dog				
14-9	4.3	4.2	4.2	4.0
14-10	4.4	4.3	4.2	3.8
14-11	4.4	4.3	4.3	4.0
14-13	4.6	4.6	4.2	4.0
14-14	5.0	4.9	4.7	4.3
14-15	5.0	4.9	4.8	4.4
14-16	4.7	4.7	4.7	4.3
14-17	4.9	4.7	4.6	4.4
14-18	4.6	4.2	4.1	3.9
14-19	4.5	4.6	4.3	3.9
14-21	4.6	4.6	4.5	4.0
14-22	5.0	5.0	4.9	4.5
Perphenazine (Trilafon, 4 mg/dog)				
14-90	4.7	4.6	4.6	4.2
14-91	4.5	4.4	4.4	3.9
14-92	5.0	4.8	4.8	4.4
14-93	5.0	4.9	4.9	4.6
14-94	4.7	4.8	4.6	4.3
14-95	4.7	4.7	4.5	4.2
14-96	4.6	4.6	4.5	4.1
14-97	4.5	4.5	4.2	3.7
14-98	4.8	4.6	4.5	4.2
14-99	4.6	4.6	4.4	4.0
14-100	5.2	5.1	5.0	4.7
14-101	4.6	4.7	4.4	4.1
14-102	4.8	4.6	4.5	4.3

Dog No.	Day of study 1	2	3	4
ASA, 2 g/dog				
14-24	4.4	4.3	4.1	3.85
14-25	4.2	3.8	3.6	3.5
14.26	3.8	3.75	3.5	3.3
14-28	4.25	4.2	3.9	3.7
14-29	DIED DURING IRRADIATION-----			
14-30	4.75	4.8	4.6	4.25
14-31	4.4	4.45	4.05	3.6
14-32	4.15	3.95	3.8	3.4
14-33	4.25	4.2	4.0	3.75
14-34	4.2	4.15	4.0	3.65
14-36	4.4	4.15	4.05	3.85
14-37	3.35	2.95	2.8	2.55
14-38	4.0	3.95	3.8	3.35
Chlorpromazine, 50 mg/dog				
14-50	4.9	5.0	4.85	4.45
14-51	4.8	4.8	4.65	4.34
14-52	4.85	4.85	4.7	4.36
14-53	5.0	5.05	4.92	4.67
14-54	4.75	4.73	4.55	4.32
14-55	4.55	4.55	4.4	4.0
14-56	4.75	4.7	4.48	4.4
14-57	4.25	4.28	4.2	3.82
14-58	4.23	4.26	3.96	3.72
14-59	4.34	4.34	4.18	3.92
14-60	4.18	4.2	4.0	3.8
14-61	4.42	4.45	4.5	4.45
14-62	4.32	4.4	4.3	4.25
Diphenhydramine HCl, 25 mg/dog				
14-76	5.0	4.9	4.6	4.4
14-77	4.8	4.7	4.6	4.4
14-78	3.6	3.5	3.4	3.2
14-79	5.2	5.2	5.0	4.9
14-80	4.8	4.6	4.5	4.3
14-82	4.6	4.5	4.1	3.9
14-83	4.2	4.1	4.1	3.9
14-84	4.4	4.3	4.2	4.0
14-85	4.7	4.6	4.4	4.1
14-86	5.0	4.7	4.7	4.2
14-87	4.3	4.2	3.9	4.7
14-88	4.7	4.6	4.6	4.2
14-89	4.5	4.3	4.3	3.8
Phenytoin Na, 60 mg/dog				
14-63	4.7	4.6	4.4	4.2
14-64	4.4	4.3	4.3	4.2
14-66	4.6	4.6	4.5	4.1
14-67	4.4	4.4	4.3	3.8
14-68	3.9	3.9	3.8	3.4
14-69	4.4	4.3	4.2	3.8
14-70	4.3	4.4	4.2	3.9
14-71	4.4	4.3	4.2	4.1
14-72	4.7	4.7	4.7	4.3
14-73	4.4	4.4	4.3	3.7
14-74	4.8	4.7	4.5	4.2
14-75	4.5	4.4	4.5	4.3

APPENDIX B (Continued)

POSTIRRADIATION BODY WEIGHT (kg) CHANGES

Dog No.	Day of study 1	2	3	4
		WR2721, 150 mg/dog		
14-43	4.65	4.4	4.55	4.25
14-44	4.0	3.8	3.7	3.7
14-45	4.3	4.05	4.0	3.6
14-46	4.8	4.53	4.45	4.4
14-47	4.3	4.24	4.0	3.8
14-48	3.9	3.65	3.55	3.55
14-49	4.4	4.35	4.25	4.0

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An animal model of irradiation-induced emesis was developed which involved exposing young male beagle dogs to 800 rads in the abdominal area. This caused a 100% incidence of emesis within 8 hr and a second wave of emesis and hemorrhagic diarrhea approximately 48 hr later. Seven drugs and one combination of two drugs were examined for effects against these responses. Chlorpromazine proved to be the most potent antagonist of first-stage emesis

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