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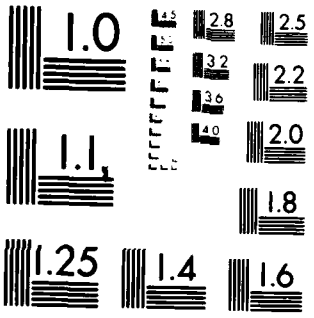

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ANTIEMETIC STUDIES BOTH PRE AND POST EXPOSURE: PRELIMINARY FINDINGS

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July 1983

Preliminary Report for Period January 1982 - October 1982

Approved for public release; distribution unlimited.

USAF SCHOOL OF AEROSPACE MEDICINE
Aerospace Medical Division (AFSC)
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NOTICES

This preliminary report was submitted by personnel of the Weapons Effects Branch, Radiation Sciences Division, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas, under job order 7757-05-38.

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

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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Initial findings of the latest testing of radiation antiemetic drug treatments are described. Four groups of random-source dogs, each with at least 13 dogs, were exposed to varying levels of radioactive cobalt using the up-down test paradigm. Cimetidine, thiethylperazine, and promethazine have been tested previously in this laboratory and have been shown to be effective, in combination, in curtailing radiation-induced emesis. Testing described herein used the same three drugs, but they were injected following radiation (group 1). Group two animals were injected with saline following radiation. Group three animals were

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20. ABSTRACT (Continued)

administered the same three drugs plus the corticosteroid dexamethasone prior to being irradiated. Group four received saline prior to irradiation. Only the combination of four drugs given prior to irradiation was effective in altering the incidence of emesis.

ANTIEMETIC STUDIES BOTH PRE AND POST EXPOSURE: PRELIMINARY FINDINGS

BACKGROUND

The Radiation Sciences Division, USAF School of Aerospace Medicine (USAFSAM), has directed and/or conducted research during the last 7 years in several aspects of the cause and control of radiation-induced emesis (1-9). This line of investigation was initiated to understand and overcome the emetic effects of radiation. Reduction of radiation-induced emesis and associated prodromal problems is beneficial to both the military and the radiation therapy community.

Dogs have been used as test subjects because they have applicable biochemical and radiation effect levels much more similar to humans than are known of other monogastric animals which vomit (4). Previous testing had demonstrated significant ability to curtail radiation-induced emesis in mixed-breed dogs with a combination of promethazine (13.92 mg/m^2 i.m.), thiethylperazine (5.57 mg/m^2 i.m.), and cimetidine (167 mg/m^2 i.v.) administered 30-40 minutes prior to gamma exposure (4). In that study the group of random-source dogs which received the combination of all three drugs had an ED_{50}[1] of 4.83 Gray (Gy)[2] with a 95% confidence interval (95% C.I.) of 4.31 to 5.43 Gy. In that same study, the group of dogs which received radiation but no drugs (control animals) had an ED_{50} of 2.58 Gy and 95% C.I. of 2.20 to 3.14 Gy. Although the drugs were selected with consideration for minimal side effect, they are in drug groups which are currently classified not to be given to flying personnel. Before expensive performance testing of these specific drugs is required, it must be determined if they are as effective when given following radiation.

A pilot study had shown some value in administering a corticosteroid prior to exposure. In that test, dexamethasone had been injected intramuscularly at the rate of 11.67 mg/m^2 approximately 30 minutes prior to exposure to ^{60}Co. The rather small test (fifteen random-source dogs) produced an ED_{50} of 3.34 Gy and 95% C.I. of 2.05 to 5.34 Gy compared to the undrugged control values of 2.68 Gy with 95% C.I. of 2.07 to 3.46 Gy. The large variability of the corticosteroid group did not permit statistical significance. When the drug was added with a combination of antiemetics, it was felt that this variability could be reduced. The drug dosage should be adequate for a beneficial cellular effect but should not produce central effects when administered on a one-time only, prophylactic basis (10). Therefore, any benefit should be free of cost in the terms of performance decrement.

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[1] ED_{50} is the radiation dose which results in the observable effect (emesis) in 50% of the subjects.

[2] 1 Gray = 100 rad.

METHODS AND MATERIALS

Fifty-four random-source adult male dogs weighing an average of 17.25 kg were used. These animals were randomly assigned to four treatment groups as follows: (1) cimetidine (Cim) 167 mg/m^2 i.v., promethazine (Pro) 13.92 mg/m^2 i.m., and thiethylperazine (Thi) 5.52 mg/m^2 i.m. all given immediately following radiation exposure; (2) saline 1 1/2 ml i.m. given immediately following exposure; (3) Cim, Pro, and Thi (doses as above) plus dexamethasone (Dex) 11.67 mg/m^2 i.m. all given approximately 40 minutes prior to radiation; and (4) saline 1 1/2 ml i.m. given approximately 40 minutes prior to radiation.

Exposures were by the AECL Eldorado 78 cobalt teletherapy unit at Brooks. Each animal received approximately 0.42 Gy/min at the midline. Exposures were carefully set up so that the brain was included in the field in each case (see Fig. 1A). As a result of this brain irradiation, often the beam was centered well up in the thoracic area; however, the 90% isodose line extended out 25 cm from the center. Each animal was observed for productive emesis for a period of 8 hours following termination of radiation.

As in previous testing (3,4,8), the design used was the up-down method (11). Radiation steps were established on a natural logarithmic basis to make testing more sensitive at lower radiation levels and to reduce samples at higher exposure levels. Doses used were 2.50, 3.03, 3.68, 4.46, 5.42, 6.58, and 7.98 Gy.[3] In this procedure, each subject's radiation dose depends on the previous subject's response. The observable response is emesis; if a subject has productive emesis, the next subject in that treatment group is exposed to one radiation step less. Conversely, if a subject does not vomit, the next subject in that group will receive the next higher radiation step. This method concentrates testing around the mean and uses fewer samples to estimate an ED_{50} (11).

The dogs were placed in the restraint box. Prior acclimation to the restraint device plus directing a fan at the face seemed to make the dogs, as a group, more calm than subjects in previous studies. All subjects were fed one can (454 g) dog food approximately 80 minutes prior to exposure. All exposures were unilateral (to the left side) to unanesthetized dogs.

The two saline-injected groups were expected to behave similarly to previous control groups (4); testing was, therefore, initiated at 2.50 Gy. It was expected that emesis would be curtailed in the two drug groups, and their testing was initiated at 3.68 Gy.

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[3]Test doses were identified in earlier testing in rad (2.5 Gy = 250 rad, etc). The logarithmic equivalents of these values are each separated by the step size of 0.193251 which was chosen as 0.035 of the natural log of 250.

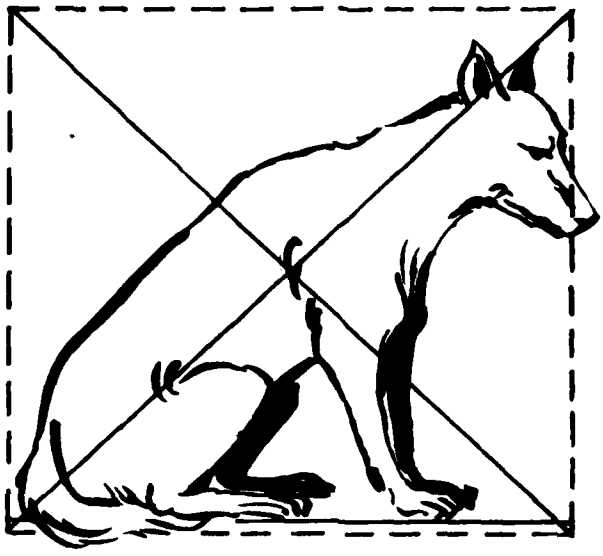

Figure 1A. Modified radiation positioning for present study. Abdomen is not as ideally irradiated, but the head is included in the field.

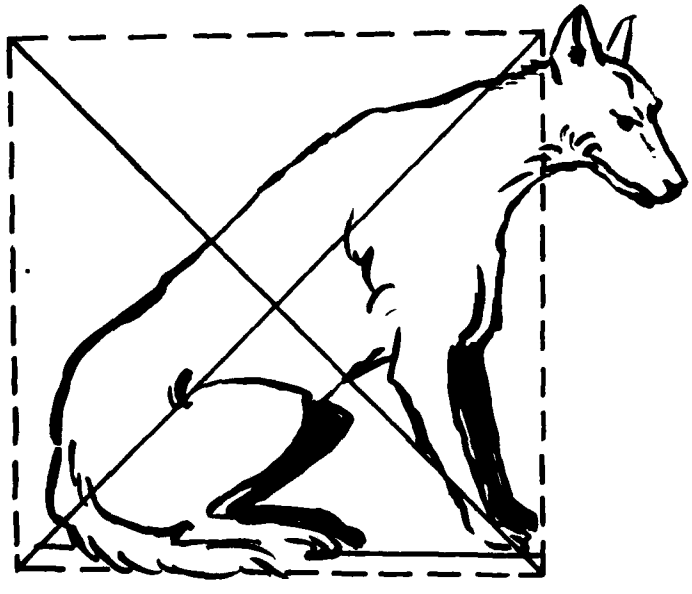

Figure 1B. Radiation positioning for previous experiments. Beam was centered over the stomach, but head was rarely included in the beam.

RESULTS

Results of the emetic activity of each animal in the two groups treated following exposure are graphically depicted in Figure 2A; results from dogs treated prior to irradiation are graphed in Figure 2B. ED_{50} dose levels, standard errors, and 95% C.I. are listed in Table 1.

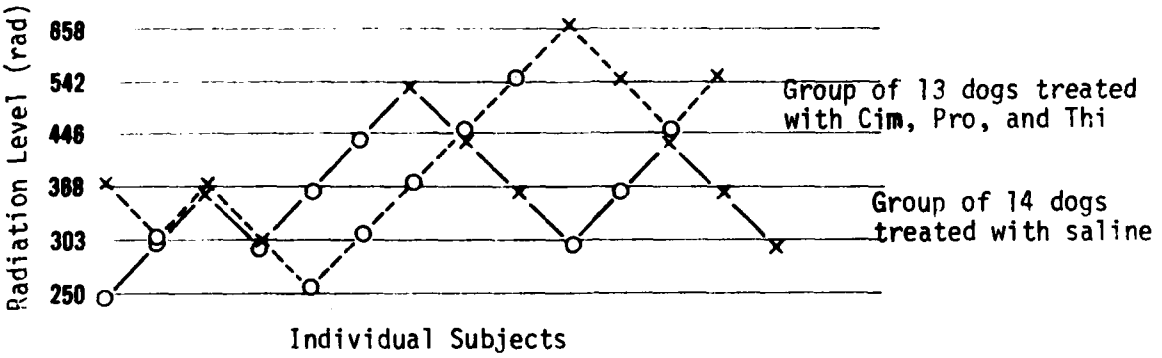

Figure 2A. Represents the emetic results of the two groups of dogs which were treated following radiation. An "X" indicates that the dog irradiated at that dose level had at least one emetic episode. A "O" indicates it had none.

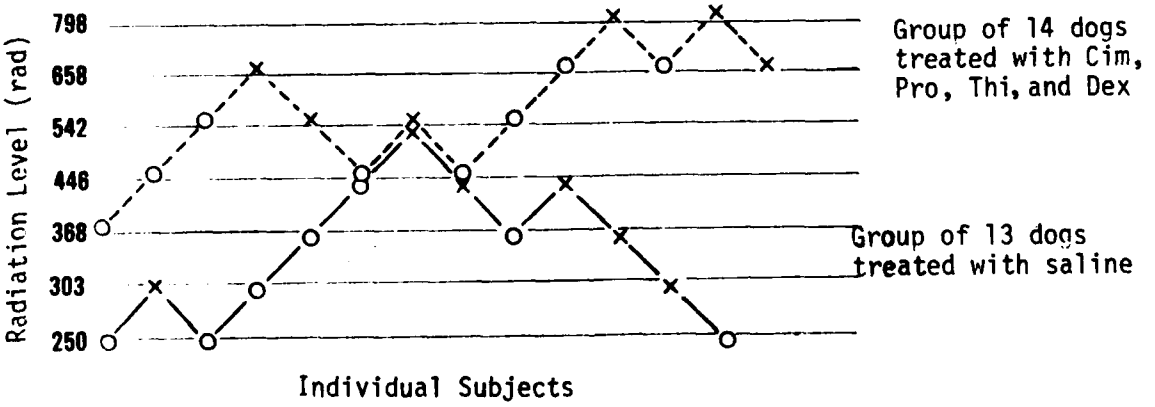

Figure 2B. Represents the emetic results of the two groups of dogs which were treated approximately 40 minutes before irradiation. An "X" indicates that the dog irradiated at that dose level had at least one emetic episode. A "O" indicates it had none.

TABLE 1. TREATMENT REGIMEN

Treatment	Time	ED_{50} (Gy)	S.E. (Gy)[a]	95% C.I. (Gy)[a]
Cim, Pro, Thi,	Post rad	4.06	1.19	2.43 to 6.77
Saline	Post rad	3.62	.37	2.98 to 4.40
Cim, Pro, Thi, Dex	Pre rad	6.01	.56	5.07 to 7.12
Saline	Pre rad	3.56	.62	2.57 to 4.93

[a]Confidence intervals are asymmetrical because of the natural log scale. Standard errors (in Gy) are worst-case estimates.

Only the combination of Cim, Pro, Thi, Dex administered before radiation was statistically different from the two saline treatments ($p < .06$). No other significant ED_{50}'s were detected.[4]

Additional data from those dogs which vomited are listed in Table 2 in the order in which they occurred in each group. This table annotates the entire sequence of events for each reacting dog. Number of episodes was most often only one. The duration of any emetic episode was only a few seconds. "Onset" indicates the number of minutes (measured from source off) at which vomiting began. Where there was more than one episode, "duration" gives the length of time during which all emetic activity took place. No emetic activity was observed in any of these animals after 6 hours, 7 minutes.

DISCUSSION

With ED_{50} results of 3.62 and 3.56 Gy, the two saline-injected groups were statistically indistinguishable one from the other. However, their ED_{50}'s were more than 1 Gy higher than the undrugged random-source dogs of Mattsson et al. (ED_{50} = 2.58 Gy). In the present study the head (brain) was included in the radiation field (Fig. 1A); in the Mattsson study (4) the cobalt exposures were limited by collimation with the beam centered at the region of the stomach. In an effort to limit restraint time for the exposure, each dog

[4]Cochran's test indicated that the group of dogs receiving Cim, Pro, Thi post exposure had a variance greater than the other three treatment groups ($\alpha = .05$). (Cochran, W.G.: The distribution of a set of estimated variance as a function of their total. Annals of Eugenics 11:47-52, 1941.) A pooled variance estimate was obtained after eliminating that group; Bonferroni's test compared the three remaining treatments. (Bonferroni's test in: Neter, J., and W. Wasserman (eds.) Applied Linear Statistical Models Sec 14.5; Richard D. Irwin, Inc., Homewood, Illinois 60430, 1974.) Satterthwaite's approximation was used to correct for the large Cim, Pro, Thi postexposure variance. (Satterthwaite's test in: Snedecor, G. W., and W. G. Cochran [eds.] Statistical Methods [7th ed.] Sec 6.11; Iowa State University Press, Ames, Iowa 50010, 1980.)

TABLE 2. EMETIC RESPONDERS DATA

Dose (Gy)	Number of episodes	Onset (min)	Duration (min)
Cim, Pro, Thi, Post Radiation			
3.68	1	137	1
3.68	4	165	82
3.03	1	197	1
6.58	1	141	1
5.42	3	109	56
5.42	17	98 ± 7[a]	169 ± 7
Saline Post Radiation			
3.68	1	367	1
5.42	16	113	100
4.46	6	138	99
3.68	1	167	1
4.46	1	190	1
3.68	1	219	1
3.03	1	164	1
Cim, Pro, Thi, Dex, Pre Radiation			
6.58	1	116	1
5.42	1	127	1
5.42	1	143	1
7.98	2	76	72
7.98	3	66	59
6.58	6	77	102
Saline Pre Radiation			
3.03	1	156	1
5.42	1	149	1
4.46	1	163	1
4.46	4	129	48
3.68	1	114	1
3.03	1	224	1

[a]Observer is physically present at all times. However, experience has shown that some dogs are able to vomit with very little physical effort, so the observer is required to look at the cage floor every 15 minutes. The first emetic episode was not observed, but was discovered to have occurred sometime between 90 and 105 minutes.

was positioned as close to the cobalt source as possible. These factors often had the effect of moving the head outside the beam during exposure (Fig. 1B). Our two saline-injected groups are within .5 Gy of the 4.12 Gy ED_{50} for mixed-breed control dogs exposed at a Reactor (8). By filtration through water, most neutrons were eliminated so that the neutron:gamma ratio was 1:14 for these tests. The average reactor gamma energy was 1.13 MeV, just less than the energy of ^{60}Co. Dose rates in all tests were similar. It appears, therefore, that head (brain) irradiation may initiate some direct neural effect which necessitates additional insult to reach the same endpoint.

Although the present experiment is not the definitive test of a direct brain radiation effect, a literature search suggested that this was a reasonable hypothesis. For instance, histamine, a well-known by-product of in-vivo radiation, was shown to activate cholinergic neurons leading to changes in dopamine metabolism (12). Rabbits exposed to 800r x-ray at 20r/min had decreased amplitude and frequency of action potentials of flexors which were caused to contract by electrical skin stimulation of the shin (13). Thus, the reflex extended to a lesser number of motor units. Additional investigation led to the conclusion that longer reflex time depends on an increase in central conduction time (14). This time increase suggests a decline in the functional activity of the spinal cord. In human EEG recordings, response was seen within 30 seconds of initiation of ^{60}Co radiation at the rate of 7.6 r/min (15).

In the present experiment the manner of irradiation was determined to assure brain inclusion in all subsequent testing until this hypothesis can formally be tested. Our results strengthen the theory that brain irradiation does reduce neural transmissibility in some fashion.

One additional complicating factor, however, is that this experiment is the second one involving gamma radiation exposures to random-source dogs which had recently been affected by symptoms of upper respiratory disease (8). In both cases the ED_{50} results of undrugged dogs were more than 1 Gy higher than a previously conducted experiment (4,8) and the 95% confidence intervals do not overlap. Although these dogs had clinically recovered from the condition, they were incorporated into testing almost immediately on release from quarantine. Some prolonged nonspecific stress response may occur similar to that which in rodents increases the LD_{50} of radiation given following skin wounds (16,17).

CONCLUSIONS

At this time, treatments given prior to irradiation appear to be more effective than when given following irradiation. Adding corticosteroid (Dex) to the three-drug combination (Cim, Pro, Thi) prior to irradiation is valuable. Compared to its saline controls, this four-drug combination raised the ED_{50} by a factor of approximately 1.7. This increase is comparable to the approximately 1.9 increase obtained in contrasting Mattsson et al.'s Cim, Pro, Thi with their parallel controls. With the liberty of comparing across experiments, however, Cim, Pro, Thi, Dex achieved the highest ED_{50} of all experimental treatments and represents a 1.24 increase in efficacy compared to Cim, Pro, Thi.

Additional samples are planned in all four groups; thus the standard error of each group should be reduced, possibly allowing detection of a significant difference of the Cim, Pro, Thi postexposure group. Also, the reduced variance would strengthen the significance of the four-drug treatment group.

The hypothesis that head (brain) irradiations raise the threshold for neural transmission thereby raising the emetic threshold should be addressed in future studies.

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