

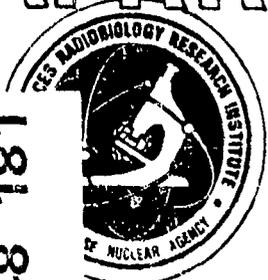
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## Altered gastric emptying and prevention of radiation-induced vomiting in dogs

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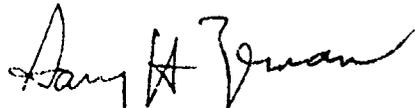
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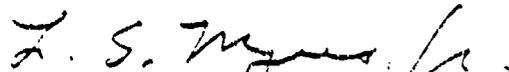
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Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals," prepared by the Institute of Laboratory Animal Resources, National Research Council.

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20. ABSTRACT (continued)

Gy (800 rads) whole-body irradiation with cobalt 60  $\gamma$ -rays after either placebo (n = 10) or domperidone (n = 10). Before each study, each dog was fed chicken liver tagged in vivo with  $^{99m}\text{Tc}$ -sulfur colloid (solid marker), and water containing  $^{111}\text{In}$ -diethylenetriamine pentaacetic acid (liquid marker). Dogs were placed in a Pavlov stand for the subsequent 3 h and radionuclide imaging was performed at 10-min intervals. Irradiation produced vomiting in 9 of 10 dogs given placebo but only in 1 of 10 dogs pretreated with domperidone ( $p < 0.01$ ). Gastric emptying of liquids and solids was significantly suppressed by irradiation ( $p < 0.01$ ) after both placebo and domperidone. These results demonstrate that radiation-induced vomiting is accompanied by suppression of gastric emptying. Furthermore, domperidone prevents vomiting produced by ionizing radiation but does not alter the accompanying delay of gastric emptying.

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## Altered Gastric Emptying and Prevention of Radiation-Induced Vomiting in Dogs

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The relation between radiation-induced vomiting and gastric emptying is unclear and the treatment of this condition is not established. We explored, therefore, (a) the effect of cobalt 60 irradiation on gastric emptying of solids and liquids and (b) the possibility of preventing radiation-induced vomiting with the dopamine antagonist, domperidone. Twenty dogs were studied on two separate days, blindly and in random order, after i.v. injection of either a placebo or 0.06 mg/kg domperidone. On a third day, they received 8 Gy (800 rads) whole body irradiation with cobalt 60  $\gamma$ -rays after either placebo ( $n = 10$ ) or domperidone ( $n = 10$ ). Before each study, each dog was fed chicken liver tagged in vivo with  $^{99m}\text{Tc}$ -sulfur colloid (solid marker), and water containing  $^{111}\text{In}$ -diethylenetriamine pentaacetic acid (liquid marker). Dogs were placed in a Pavlov stand for the subsequent 3 h and radionuclide imaging was performed at 10-min intervals. Irradiation produced vomiting in 9 of 10 dogs given placebo but only in 1 of 10 dogs pretreated with domperidone ( $p < 0.01$ ). Gastric emptying of liquids and solids was significantly suppressed by irradiation ( $p < 0.01$ ) after both placebo and domperidone. These results demonstrate that radiation-induced vomiting is accompanied by suppression of gastric emptying. Furthermore, domperidone prevents vomiting produced by

ionizing radiation but does not alter the accompanying delay of gastric emptying.

Exposure to high levels of ionizing radiation produces a constellation of signs and symptoms that characterize radiation sickness (1). These symptoms occur after latency periods that vary with the system involved and the dose received. If the dose is sufficiently high, a hematopoietic syndrome will develop after a few days, and can be either temporary or permanent. If the dose is even higher, a major gastrointestinal syndrome will appear after 6-10 days, characterized by diarrhea and melena. This acute and subacute syndrome is clearly different from the long-term effects of irradiation, which will not be discussed in the present paper.

During the first hours after exposure to ionizing radiation and before any of these life-threatening symptoms do appear, a prodromal syndrome characterized by nausea and vomiting is commonly observed. These symptoms can occur after total body exposures of 1 Gy (100 rads) or more, and usually disappear after a few hours (2). The pathophysiology of this syndrome as well as the concurrent motor activity of the stomach are largely unknown.

In the present studies, we examined the correlation between gastric function and vomiting after irradiation by studying three different aspects of the prodromal syndrome in dogs. First, we evaluated the possibility of producing vomiting after total body irradiation with cobalt 60  $\gamma$ -rays. In addition, we determined the effect of total body irradiation on the rate of gastric emptying of solid and liquid food. Finally, we examined the effect of an antiemetic agent, domperidone, on radiation-induced vomiting and on gastric emptying.

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Abbreviations used in this paper: CTZ, chemoreceptor trigger zone; ROI, regions of interest; VC, vomiting center.

## Materials and Methods

The design of the study was as follows. On three separate days and after an overnight fast, 20 male beagle dogs weighing 10–13 kg were given, and ate avidly, a mixed solid-liquid meal consisting of 500 g of canned meat to which were added (a) 10 g of raw chicken liver labeled in vivo with 37 MBq (1.0 mCi)  $^{99m}\text{Tc}$ -sulfur colloid (3) and (b) 50 ml of tap water containing 37 MBq (1.0 mCi) of  $^{111}\text{In}$ -diethylenetriamine pentaacetic acid (DTPA). Immediately thereafter, the dogs were placed in a Pavlov stand, and received an intravenous injection of either placebo or domperidone (0.6 mg/kg) given blindly and in random order. The dogs were then placed in front of a small field of view  $\gamma$ -camera (12-in. diameter) with a medium energy collimator, which was interfaced with a PDP (programable data processor) 11/45 computer. Two 1-min static images covering the dog's entire abdomen were acquired successively for both the left and right sides, 45 min after the start of the meal, which was taken as time zero.

On the 2 days of the baseline studies, each animal was then brought to the exposure room after receiving either domperidone or placebo, but no radiation was given (sham irradiation). Thus, during the first baseline study, 10 dogs received placebo and 10 dogs received domperidone. During the second baseline study, the 10 dogs that had received placebo received domperidone and vice versa. On the day of the irradiation study, total body irradiation was administered 10–20 min after the intravenous injection of either domperidone or placebo. Two sets of sources of cobalt 60 were placed at 100 cm on each side of the animal, producing a dose rate of 8 Gy (800 rads) per minute in air. Dosimetry and phantom studies demonstrated that a dose of 8 Gy was received in the midline abdomen, whereas the midline brain was exposed to 6 Gy (600 rads). This design allows evaluation of (a) the effect of domperidone during the baseline study in all 20 animals and (b) the effect of irradiation in the presence or absence of domperidone.

After returning from the exposure room within 10 min of either the sham or the actual irradiation, the animals were again placed in front of the  $\gamma$ -camera and radionuclide imaging was performed at 10-min intervals for a period of 3 h. The animals were then taken back to their cages and were closely observed during the subsequent 3 h. Thus, the dogs were watched for a total of 6 h and any abnormal behavior or vomiting was recorded. Vomiting was defined as the spasmodic expulsion of radioactive material from the mouth. If vomiting was observed, imaging was discontinued, but the animals continued to be observed for the usual duration of the experiments.

The images stored on disk were subsequently analyzed by defining regions of interest (ROI) corresponding to the stomach and intestines on a video screen. The amount of radioactivity in each ROI was calculated using a PDP 11/45 computer. During the acquisition of images, we used peak energies of 140 keV for  $^{99m}\text{Tc}$  and of 247 keV for  $^{111}\text{In}$ . We verified that using a 20% window with these peaks prevented any overlap of  $^{99m}\text{Tc}$  into the  $^{111}\text{In}$  window; however, the low energy peak of  $^{111}\text{In}$  (171 keV) and its Compton scatter into the Tc window required correction.

Preliminary in vitro and in vivo studies demonstrated that approximately 40% of the  $^{111}\text{In}$  counts spilled into the Tc window. Therefore, 40% of the In counts were subtracted from the Tc counts in each ROI. A decay correction was then applied to each isotope for each ROI. The geometric means of the corrected  $^{99m}\text{Tc}$  and  $^{111}\text{In}$  counts were then calculated for the gastric and intestinal regions of interest in the right and left images. These mean counts for stomach and intestine were then added and the percentage of the total counts of  $^{99m}\text{Tc}$  and  $^{111}\text{In}$  present in the stomach was calculated at each 10-min interval. The gastric fractional emptying rate, which is the slope of the exponential decline of the intragastric contents of each isotope, was then determined for each animal. In each group, mean values for these fractional emptying rates ( $\pm$ SEM) were calculated. The statistical significance of differences between groups was determined using  $\chi^2$  and paired *t*-tests.

## Results

During the baseline studies, domperidone did not produce any noticeable abnormal behavior, motor deficit, or coordination problems. Similarly, domperidone did not significantly modify gastric emptying of liquids (Figure 1) or solids.

In contrast, irradiation produced vomiting in 9 of 10 dogs as well as a significant ( $p < 0.01$ ) delay in the gastric emptying of liquids after administration of a placebo (Figures 2 and 3). Similarly, gastric emptying of solids was significantly ( $p < 0.01$ ) suppressed after radiation (Figure 4). This delay in emptying was as prominent in the irradiated animal who did not vomit as it was in those who did.

When an injection of domperidone was given before radiation exposure, vomiting was observed in only 1 of 10 dogs ( $p < 0.01$ ), but gastric emptying of both liquids and solids was still significantly delayed in all animals (Figures 3 and 4).

## Discussion

These data demonstrate that total body irradiation with cobalt 60  $\gamma$ -rays produces emesis in 90% of the dogs exposed to 8 Gy. These results are consistent with those of Cooper and Mattsson (4), who showed that the  $\text{ED}_{50}$  for vomiting was 1.7 Gy. The exact mechanism by which irradiation produces this effect is unknown. In humans, vomiting may be induced by irradiation of various parts of the body, although the effect is greater after exposure of the upper half of the body than after exposure of the lower half (5). Similarly, in rats, irradiation-induced anorexia is most prominent after exposure of the intestines, whereas irradiation of the head or limbs is less effective (6). Nonetheless, radiation may still elicit vomiting after complete excision of the stom-

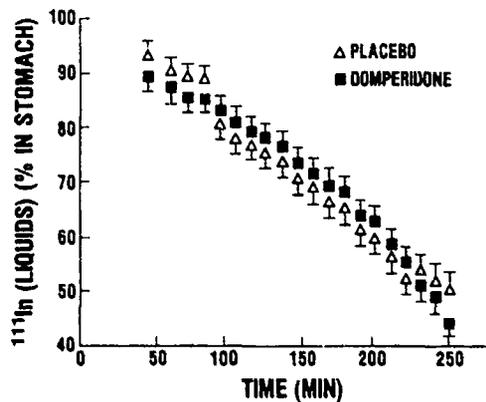


Figure 1. Effect of domperidone on emptying of liquids during baseline studies. Values are means  $\pm$  1 SEM.

ach, small intestine, and colon (7). Radiation-induced vomiting is prevented by the surgical resection or thermal coagulation of an area of the medulla located immediately under the floor of the fourth ventricle, the chemoreceptor trigger zone (CTZ) (8,9). In contrast, shielding of the CTZ does not prevent vomiting (10). Based on these observations, it is possible that ionizing radiations stimulate the CTZ indirectly, either through the activation of the peripheral end of afferent nerves or through the release of one or several humoral factors. By analogy with vomiting produced by apomorphine and certain cardiac glycosides, the CTZ would then send impulses to the vomiting center (VC), which is located in the lateral reticular formation. The VC would then initiate the complex motor events characterizing retching and vomiting.

The present results also demonstrate that gastric emptying of liquids and solids is suppressed within 2 h of exposure to ionizing radiation. Such a suppression of emptying after irradiation had been previously reported only in rodents, a species that does not vomit (11-13). In the dog, gastric emptying was found to be normal 2 and 3 days after irradiation, but

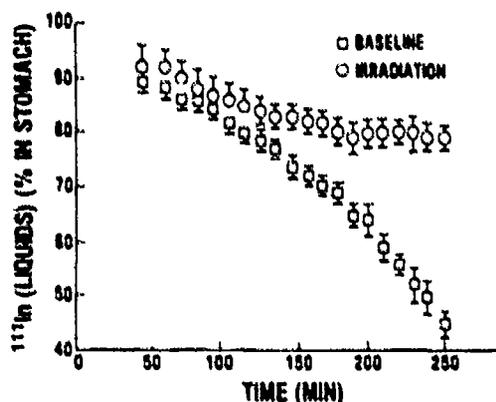


Figure 2. Effect of irradiation on emptying of liquids. Values are means  $\pm$  1 SEM.

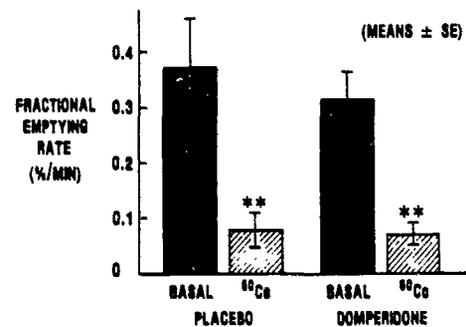


Figure 3. Effect of irradiation ( $^{60}\text{Co}$ ) and domperidone, alone or in combination, on the fractional emptying rate for liquids. \*\* $p < 0.01$  compared with corresponding baseline study.

no study was done on day 1 (14). The mechanism of this effect is unclear. Vomiting produced by apomorphine or other stimuli is preceded by slowing of the pacesetter potentials (slow waves), suppression of the spiking activity (15), and relaxation of the stomach, the latter being abolished by vagotomy (16,17). Apomorphine-induced vomiting is also preceded by initial suppression of the electrical activity of the duodenum, followed by bursts of antiperistaltic activity (18,19). These effects produce gastric relaxation, increased intraduodenal pressures (20), and, consequently, a delay of gastric emptying. These changes in gastrointestinal activity after apomorphine administration are likely to be induced by central mechanisms involving the central vagal nuclei, which are in the immediate vicinity of the CTZ and VC. It is possible, therefore, that stimulation of afferent nerves or the release of humoral factors that cause radiation-induced vomiting are also responsible for the activation of the vagal nuclei or other central nervous system centers. In turn, these centers would delay gastric emptying either through the stimulation of the inhibitory fibers of the vagus nerve (16) or through the release of humoral agents.

Our studies demonstrate that domperidone does not prevent the radiation-induced suppression of

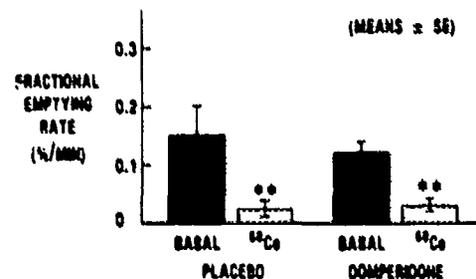


Figure 4. Effect of irradiation ( $^{60}\text{Co}$ ) and domperidone, alone or in combination, on the fractional emptying rate for solids. \*\* $p < 0.01$  compared with corresponding baseline study.

gastric emptying. In contrast, domperidone was shown to suppress the delay of gastric emptying induced by apomorphine (21) or dopamine (22), as well as to improve gastroduodenal coordination in the isolated perfused guinea pig and rat stomach (23,24). Our observation, therefore, indicates that the dopaminergic receptors of the CTZ or of the stomach are not involved in the radiation-induced delay of gastric emptying. In addition, since the radiation-induced delay of gastric emptying was not improved when vomiting was suppressed by domperidone, it appears that the two symptoms are independent of each other. Alternatively, the dopamine receptors involved in the two phenomena may have a different sensitivity threshold.

In the present studies, preirradiation administration of domperidone was found to effectively prevent the vomiting caused by ionizing radiation. This effect is similar to that produced by resection of the CTZ (8) and is compatible with a direct effect of the drug on that area of the brain. Indeed, domperidone has been shown to bind with cerebral dopaminergic receptors. When given intravenously or orally, however, its concentrations in the medulla, cerebellum, and thalamus are threefold those found in the striatum or cortex (25). Domperidone, therefore, could act on the CTZ, but is relatively devoid of extrapyramidal side effects such as the ones observed after administration of other antidopaminergic agents, such as haloperidol or metoclopramide. In addition, contrary to neuroleptic agents, it does not modify the state of vigilance. Thus, domperidone could be used to prevent radiation-induced vomiting. One study performed in humans (26) has suggested that domperidone was indeed effective in decreasing nausea and vomiting encountered during radiotherapy. Unfortunately, no double-blind design was used, and this shortcoming may be very important in a situation where psychologic factors are known to be very important. Thus, additional studies should be performed in humans using double-blind administration of domperidone and other anti-nauseating agents or placebo.

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