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● *Original Contribution*

EVALUATION OF DOMPERIDONE AS A MODIFIER OF GAMMA-RADIATION-INDUCED EMESIS

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The D_2 antidopaminergic drug domperidone was evaluated, singly and in combination with synthetic adrenocorticoid and an H_2 antihistamine, for its ability to reduce the acute emetic effects of ^{60}Co whole-body radiation. Random-source adult male dogs were fasted 12 hr, fed a standard meal, injected 44 min later, and irradiated 47 min after that. Four groups of dogs were irradiated after drug injections as follows: saline (Con), domperidone (Dom), cimetidine + thiethylperazine (Cim+Thi), and dexamethasone + domperidone + cimetidine (Dex+Dom +Cim). Drug quantities given the dogs represented 10 mg Dom, 10 mg Thi, 20 mg Dex, and 300 mg Cim for an average human (70 kg, 1.8 m^2). Subjects were exposed on an up-down schedule to determine the radiation necessary to produce vomiting in 50% (ED_{50}) of each group. Emesis onset and offset times and number of episodes were recorded. The Dom group had more emetic episodes than any other. The Dex+Dom+Cim combination significantly raised the emetic threshold while maintaining episodes at a low incidence.

Gamma radiation, Emesis, Drugs, Antidopaminergic, Domperidone, Cimetidine, Dexamethasone, Dogs.

INTRODUCTION

Tranquilization can be an undesirable side effect when drugs are administered to off set anticipated prodromal symptoms of radiation therapy. While conducting several experiments to combat acute radiation effects, our laboratory's driving consideration has been prophylaxis with minimal to no side effects.[12–14,24,31,32]

Early research indicated that the chemoreceptor trigger zone (CTZ) is essential in the postradiation emetic response.[9] The CTZ is located bilaterally in area postrema outside the blood-brain barrier. Also, when placed on area postrema, dopamine and its main agonist apomorphine will produce vomiting. Certain phenothiazines (chlorpromazine is the prototype) will counter the action of these two bioamines.[7] Both H_1 and H_2 histamine receptor sites also produce vomiting at area postrema,[3] but the H_1 prototype antagonist mepyramine and the H_2 prototype antagonists burimamide or metiamide will counter the presence of histamine here.

Work in our laboratory has demonstrated that the same pharmacologic groups are also active in radiation-induced vomiting.[12,24,31,32] To find drugs that would combat the acute radiation effects but have insignificant psychoactive side effects, we chose different antagonist drugs in the same groups. Some investigators have found thiethylperazine (phenothiazine-derivative antidopaminergic) to be effective against therapeutic radiation in people[6,11] and in dogs.[12,32] Some have successfully used antihistamines as antiemetics for human radiation therapy,[30,35] but others have found them to be ineffective[36]; the antihistamines used in those studies were the type active at H_1 receptor sites. Both H_1 and H_2 receptors are present in the CNS, and Douglas[17] has suggested that two antihistamines active at both H_1 and H_2 sites sometimes act in a synergistic fashion. A study with radiation and combined drugs in dogs indicates they may be at least additive.[32] In that study the ED_{50} level (radiation required to cause emesis in 50% of subjects) after combined H_1 and H_2 antihistamines was higher than ED_{50} levels after either alone.

Corticosteroids are useful with a variety of tissue insults, including radiation.[26] With a single administration of most steroids, detrimental side effects are unlikely.[1]

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Two animal experiments have suggested that steroids help raise the emetic ED_{50}.[14]

Some drugs have produced nearly 2-fold levels of protection against acute radiation side effects in dogs. In one study thiethylperazine (Thi), cimetidine (Cim), and promethazine (Pro), used together, raised the ED_{50} 88% (4.83 Gy compared to 2.57 Gy in the control group).[32] In a later study dexamethasone (Dex) was added; the ED_{50} of the treated group was raised 69% (6.01 Gy versus 3.49 Gy of the controls).[14] In humans, performance testing with Cim, Pro, and Thi showed Pro to be decremental.[37]

As with histamines, at least two types of dopaminergic receptors are important in producing emesis.[15] Major brain centers activated by dopamine are rich in receptors classified as D_1. Dopamine fully activates these receptors, apomorphine moderately so; and phenothiazines antagonize them. D_2 receptors are also in the CNS (corpus striatum at least) but predominate peripherally (including CTZ and stomach). Dopamine and apomorphine fully activate the D_2 receptors, and phenothiazines strongly antagonize them. A new class of drugs, butyrophenones, also strongly antagonize D_2 receptors but weakly affect D_1 receptors. Domperidone belongs to the butyrophenone class.

Domperidone specifically counters nausea and vomiting induced by locally and/or centrally acting dopamine agonists and also corresponds with a myoelectric abnormality at antrum and proximal intestine.[34] Because domperidone does not cross the blood brain barrier, it causes no central effects.[29]

We have used dogs in our experiments because the literature indicates that they closely resemble humans in their acute radiation response.[12] Of monogastric animals known to vomit, inadequate information is available on radiation response of the pig, cat, and ferret. Common animals left to consider were the dog and monkey. Radiation LD_{50} and emesis ED_{50} values are similar between dogs and humans, while the rhesus monkey requires more radiation for these reactions. In the CTZ, as the dog and human have similar radiation response, so they have similar responses to apomorphine; but a response in the monkey requires very high doses. Also, normal plasma histaminase values are high in monkeys but more moderate in dogs and humans.[23]

Most of our research has used random-source dogs in an up-and-down exposure sequence. With this procedure we used fixed drug dosages and varying radiation doses. Each animal received a radiation exposure based on the emetic result of the preceding animal in that group. When one subject in a treatment had emesis, we gave the next subject one step less of radiation. Conversely, when a subject failed to display emesis during the observation period, we gave the next subject one step more of radiation. This procedure uses fewer animals than standard probit techniques to estimate the dose of radiation needed to cause emesis in 50% of subjects in each treatment group (ED_{50}).[16]

METHODS AND MATERIALS

Our procedure was similar to that described by Cooper and Mattsson[12]; the following is a summary. We used conditioned adult, male, random-source dogs averaging 16.4 kg. During holding they received a dry ration in the morning and had water available at all times. On test day each animal received only one can (450 gr) of commercial dog food. About 44 minutes later (range 30–70 min) they received drug injections according to their random assignment to the drug groups. Each test day no more than one animal was run in each test group.

Table 1 shows the drugs* and quantities injected. Drug dosage was equated to body surface area to most evenly relate dosage in the different sized dogs and to have comparability with man. The doses represent for a 70-kg man, 10 mg domperidone (Dom), 300 mg Cim, 10 mg Thi, and 20 mg Dex. The surface area of each dog[22] was calculated by the formula $m^2 = 10.1 \times (\text{weight in gm})^{2/3} \times 10^{-4}$; 1.8 m^2 is the surface area for a 70-kg man.

The dogs received ^{60}Co radiation exposure 47 minutes after injection (range 32–83 min). For irradiation, each was confined, conscious, in a box constructed of 0.95-cm-thick Lucite, 62 cm high, 115 cm long, with the width adjustable down to 14 cm. The dogs were placed in a seated position and held in place by 0.95-cm-thick Lucite rods placed through holes predrilled in the sides of the box.

Radiation was administered with a cobalt unit.† The step size for the up-down procedure was 0.65 Gy. The control group entered the test paradigm at 3.2 Gy, Cim +Thi at 4.5 Gy, Dom at 6.45 Gy, and Dom+Dex+Cim at 7.1 Gy. Exposures ranged from 2.55 to 7.1 Gy, and the rate was approximately 0.28 Gy/min.

Table 1. Drug combinations and quantities used

Compound	Subjects	Quantity	Route
Saline (control)	15	1 ml	i.m.
Domperidone	15	5.6 mg/m^2	i.m.
Cimetidine	14	167 mg/m^2	i.v.
Thiethylperazine		5.6 mg/m^2	i.m.
Domperidone	15	5.6 mg/m^2	i.m.
Cimetidine		167 mg/m^2	i.v.
Dexamethasone		11.1 mg/m^2	i.m.

* Domperidone was provided by Janssen Pharmaceutica, Inc.; 40 Kingsbridge Rd., Piscataway, N.J., 08854. All other materials were purchased through commercial sources.

† Atomic Energy of Canada, Ltd. Eldorado Model 78.

After irradiation each dog was placed in an observation cage large enough to allow free movement. For 7 hr they were continuously observed for emesis. In all cases emesis included oral expulsion of food or mucous, with or without retches. Onset time was the number of minutes after conclusion of radiation at which the first emetic episode occurred. Each episode lasted less than 1 minute. When an animal had more than one episode, the number of minutes between the first and last episodes was given as the duration of emesis.

We used results initially to compute the ED_{50}s and their 95% confidence intervals (95% C.I.).[16] In all two-way comparisons of treatments, we used Bonferroni's multiple-comparison procedures to compare ED_{50} values ($\alpha = .10$).[5] Prior to any multiple comparisons, however, we used Cochran's C-test[10] to determine that variances of groups being compared were homogeneous. We evaluated all other results—episodes, onset, and duration—by the nonparametric multiple-comparison procedures of Dunn ($\alpha = .10$).[20]

RESULTS

Figure 1 a and b shows the results by group and experiment day. All 59 subjects are represented in their respective groups. From the results, we calculated ED_{50} values for each treatment; these are listed in Table 2.

Variances for each treatment group, compared by Cochran's C-test, were not different at the 0.05 level of significance. With Bonferroni's two-way testing of ED_{50} values, Dom+Dex+Cim had a higher value than the controls, $p < .10$; the contrast between Dom+Dex+Cim and Cim+Thi was nearly significant at the 0.10 level.

Table 3 shows the average (± standard error) number of episodes, onset times, and duration times. Episodes was the only variable in which we found significant effects. When all treatment groups were compared with controls, the Dom group averaged significantly more episodes than Con, $p < .05$; the treated groups were compared against each other and Dom had more episodes than the three-drug combination (Dom+Dex+Cim), $p < .10$.

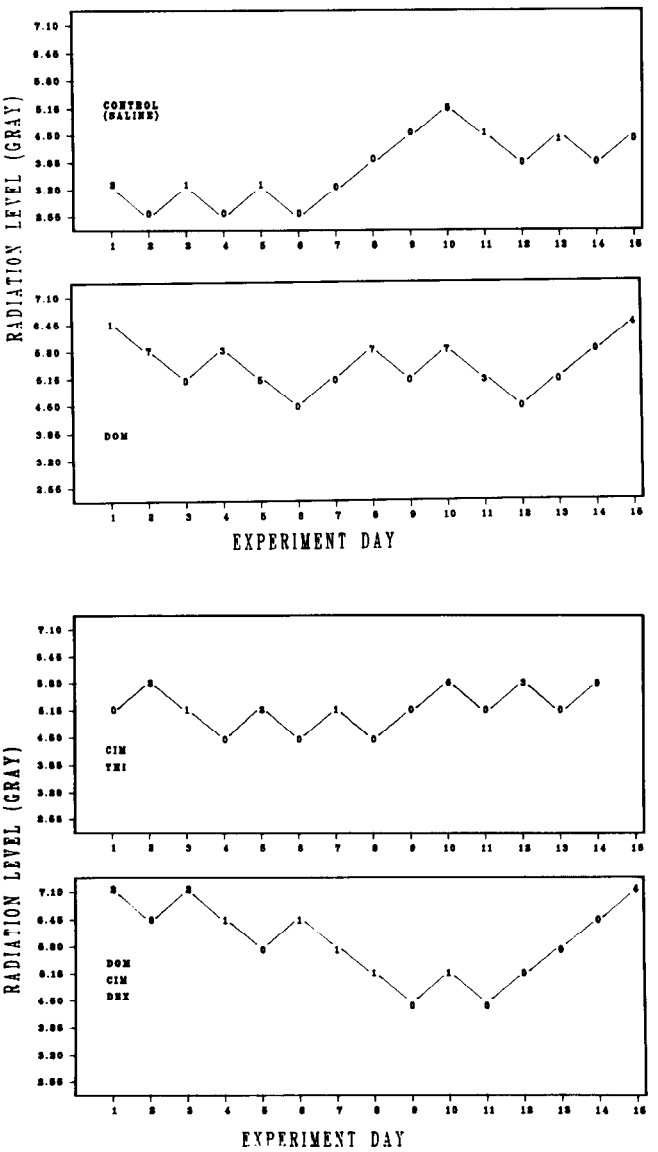

Fig. 1 (a and b). All subjects are represented in these plots. A number represents the emetic episodes of that subject as occurred by drug group and experiment day. As illustrated in any plot, in the up-down procedure, emesis for one subject results in lower exposure for the next subject.

DISCUSSION

Domperidone combined with steroid and H_2 antihistamine (Dex+Dom+Cim) provided protection against gamma-induced radioemesis in dogs. Comparison of ED_{50} values showed that a 61% increase in radiation was required to produce an effect in the triple-drug group similar to that in the Con group. (Other drug combinations that had provided similar or better increases in protection for dogs had included promethazine, a drug since shown to produce performance decrement in humans.[37] By our testing, the next best drug combination to combat acute radiation effects was Cim+Thi.[32]

The Cim+Thi combination was included in this testing so we could directly compare it with the new candidate, Dom, singly and in combination. Statistically the Dex+Dom+Cim ED_{50} results were nearly significantly better than Cim+Thi at the .10 level.

The ED_{50} (4.46 Gy) from a previous study of the Cim +Thi combination[32] is indistinguishable from our current result of 4.50 Gy. Control groups from the same two experiments are not nearly so comparable with the most recent ED_{50} at 3.63 Gy and the previous saline injected group's ED_{50} at 2.58 Gy.[32] (Even with the 1-Gy difference, the ED_{50}s taken by themselves are not statistically different.) Dose-rate effects could be playing a part in the apparent difference in these Con ED_{50}s.

Another research group used dogs to study Dom and

Table 2. Results of antiemetic therapy

Treatment group	N	$ED_{50} \pm SE$ (Gy)	95% C.I. (Gy)	Total episodes
Con	15	3.63 ± .72	2.22–5.04	11
Dom	15	5.38 ± .26	4.86–5.90	37
Cim+Thi	14	4.50 ± .16	4.18–4.81	15
Dex+Dom+Cim	15	5.85 ± .62	4.63–7.06	13

Table 3. Means ± SE for emetic responders

Treatment group	N	Episodes	Onset (min)	Duration (min)
Con	6	1.83 ± .65	141.7 ± 18.1	27.7 ± 18.7
Dom	8	4.63 ± .80	100.5 ± 11.5	75.8 ± 15.3
Cim+Thi	6	2.50 ± .76	141.0 ± 18.3	64.8 ± 38.7
Dex+Dom+Cim	8	1.63 ± .38	121.8 ± 17.1	34.9 ± 18.7

radiation.[19] With a radiation dose rate of 8 Gy/min in air, Dom (0.6 mg/kg i.v.) curtailed vomiting in 90% of animals given an 8-Gy midline dose. In clinical studies, acute symptoms associated with dose-rate effects are seldom quantified. In looking elsewhere for dose-rate effects, lethality of cell cultures is well studied in our range of radiation dose and dose-rate. Statistical differences are often found, but the difference comprising significance is only a few percentage points.[25] On the other hand, at dose rates used in our various studies, the immune response of mice showed more radiation dose-rate sensitivity.[8] In the study reported here, the dose rate effect cannot be fully appreciated.

Domperidone has produced nearly universal benefit in all tests as an antiemetic following cancer chemotherapy,[18,33] surgery,[4] and other conditions.[21] However, the most statistically significant finding of our current study is that when used alone, Dom allowed more emetic episodes than occurred in saline-injected controls. This does not necessarily indicate that the drug is unsatisfactory as an antiemetic with radiation for dogs. One limited reference to the use of Dom for radiotherapy patients describes the drug's benefit as "excellent" or "good" in 80% of trials.[2] Those positive results still allowed some incidence of nausea or vomiting. Testing by the up-down method demands vomiting in 50% of subjects in each group. While dogs in those Con and Dom groups did not have statistically different ED_{50}s, no dogs in the Dom group vomited at radiation doses below 5.15 Gy, but no dogs in the Con group were exposed above that level (See Fig 1). As suggested by our previous work,[32] a drug with some ability to raise the emetic threshold may lead to increased incidence of emesis once the threshold is exceeded. Table 2 shows that the current Con group's ED_{50} had a large variance, as has been seen before, and the Dom group had a much lower variance. So although the Dom ED_{50} was not statistically improved over the Con's and the drug allowed more episodes, we continue to interpret these results as indicating that Dom produced a rather uniform, probably maximal, effect.

The three-drug combination had a significantly higher ED_{50} than the Con's. The 61% benefit was not startling—we have seen more value in other drug combinations, but they included a performance-decrementing compound, promethazine. Dex, Dom, and Cim should be free of CNS effects. If the hypothesis is true that a large variance indicates incomplete action on available receptors,[32] this triple-drug treatment can probably be made more effective. In quest of this goal, the antihistamines should be considered first. The H_2 antihistamine by itself has allowed large variability[32] but is not now complemented by an H_1 antihistamine. Terfenidine, Merrell-Dow Pharmaceuticals, should be evaluated to fill this need.

Besides raising the emesis threshold, Dex+Dom+Cim also allowed fewer episodes than did Dom alone. None of our other drug combinations have allowed such a small number. Under the influence of the triple drug, emetic activity tended to last a relatively short time (in agreement with the fewer number of episodes). When we compared all groups, however, durations of effect were not significantly different.

Intramuscular injection of 10 mg of Dom has allowed peak plasma levels of 40 ng/ml in humans by 30 min.[27] The same quantity administered orally also reached peak plasma values (23 ng/ml) in that time, but the bioavailability was only about 16% of the parenteral route. After oral dosing, the excellent clinical results observed in a variety of gastrointestinal mobility problems suggested direct, local action on dopaminergic receptors with the process of digestion.[27] Bioavailability increased linearly over the 10- to 60-mg of Dom given orally, with no indication of untoward side effects at the higher levels.

Dosing in various amounts and routes has led to similar plasma levels and bioavailability in man and dogs.[28] The suggestion of direct, local action of Dom indicates possible benefit from its administration immediately after radiation.[27] This may be as important as the most important finding of our study—that Dex+Dom+Cim produced a significant ED_{50} increase and also maintained a low rate of episodes.

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