Effects of Dimenhydrinate and Diphenhydramine on Apomorphine-Induced Emesis in Dogs and Cats.* (20141)

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Despite the wide use of dimenhydrinate (Dramamine) and diphenhydramine (Benadryl) as anti-emetics, almost nothing is known about their mechanism of action. In many experimental studies on the problem, apomorphine has been used as the emetic stimulus. Wang and Borison(1) have found that apomorphine does not act directly on the medullary vomiting center but through the closely situated chemoreceptor trigger zone. This introduces one more possibility for the site of the alleged protective action of Dramamine and Benadryl against drug-induced vomiting. Such a possibility is strengthened by the recent finding of Wang and Chinn(2) that destruction of the chemoreceptor trigger zone in dogs prevents motion-induced vomiting. However, before the intimate mechanism of action of these anti-emetic agents can be elucidated, it is necessary to delineate accurately their specific effects in apomorphine-induced emesis. Chen and Ensor(3) reported a significant reduction in the severity but not in the incidence of apomorphine-induced vomiting in dogs pretreated with Dramamine or Benadryl. Similar results were subsequently published by Ducrot and Decourt(4). On the other hand, White and coworkers(5) reported *complete* protection with these drugs against apomorphine-induced vomiting in dogs. In contrast, Moser(6) failed to find any inhibition of vomiting induced in dogs by either subcutaneous apomorphine or oral copper sulfate. Similarly, Freese and associates(7) have reported no protection by Dramamine against morphine-induced emesis in dogs. (Presumably, the emetic action of morphine is identical with that of apomorphine.) Mitchell(8), in experiments on 3 cats, found that the emesis induced by subcutaneous apomorphine was prevented by Dramamine in 13 out of 15 trials, whereas Benadryl afforded protection in only 2 out of 12 trials.

The series of experiments reported herein was performed on dogs in which individual intravenous emetic threshold doses of apomorphine were carefully determined so that each animal could serve as its own control for subsequent tests with Dramamine‡ and Benadryl.§ In addition we attempted to confirm certain experiments, reported in the literature, which were interpreted as demonstrating that these agents afforded protection against apomorphine-induced emesis.

Methods. Five dogs were tested to determine the minimal, individually effective i.v. dose of apomorphine which consistently evoked emesis. The appropriate dose of apomorphine HCl was given in approximately one ml of a freshly made aqueous solution of apomorphine, injected rapidly into the saphenous vein. Tests were performed never more often than every third day on any one animal. The dog was fed a ration of horsemeat a few minutes before the experiment and nothing short of the actual expulsion of vomitus was considered a positive reaction to the injected apomorphine. Ten μg/kg apomorphine was used as the first dose; if this was effective, the dose was reduced to 7.5 or 5 μg/kg. On the other hand, if emesis did not occur following the initial dose of apomorphine, it was increased to 20 μg/kg. The threshold emetic dose in each animal was determined on the basis of at least 3 successive positive results. To test for anti-emetic activity of Benadryl and Dramamine, these agents were administered intravenously 15 min prior to the threshold dose of apomor-

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‡ Dramamine was supplied by G. D. Searle & Co.

§ Benadryl was supplied by Parke Davis & Co.

TABLE I. Determination of Emetic Threshold to I.V. Apomorphine in 5 Dogs.

.005 mg/kg			.0075 mg/kg			.01 mg/kg			.02 mg/kg		
Latent period, min.	sec.	Paroxysms	Latent period, min.	sec.	Paroxysms	Latent period, min.	sec.	Paroxysms	Latent period, min.	sec.	Paroxysms
	*		—		0	2	30	1	1	20	3
						—		0	1	40	3
						1	5	4	1	30	4
	*		—		0	—		0	1	30	1
						1	30	2	1	10	1
									1	20	1
—		0	—		0	1	0	2	1	40	3
						—		0	1	30	1
						2	0	1	1	30	1
—		0	0	45	4	0	40	2		*	
			0	45	3						
			0	45	3						
2	0	1	1	50	1	1	25	3		*	
—		0	2	0	1						
			1	15	1						

* Not tested.

TABLE II.
Effect of Dramamine and Benadryl on Apomorphine-Induced Emesis in 5 Standardized Dogs.*

Threshold dose of apomorphine, mg/kg	Latent period of vomiting induced by threshold dose of I.V. apomorphine											
	Control,		After I.V. Dramamine dose						After I.V. Benadryl dose			
			2 mg/kg,		5 mg/kg,		10 mg/kg,		1 mg/kg,		2.5 mg/kg,	
	min.	sec.	min.	sec.	min.	sec.	min.	sec.	min.	sec.	min.	sec.
.02	1	30	1	20	1	50		†	1	30	0	40
.02	1	20	0	50	1	50	1	30	1	0	1	5
.02	1	35	1	20	1	10		†	1	30	1	35
.0075	0	45	0	35		†	1	0	1	15		†
.0075	1	40	2	5	1	25		†	1	15	1	0

* Same dogs and order as in Table I. † Not tested.

phine. *Additional experiments* were performed on dogs and cats in the attempt to reproduce certain results, reported in the literature, obtained with the above-mentioned drugs. The methods described in these reports were duplicated as faithfully as possible. The specific technics employed are outlined in the appropriate discussions below.

Results. The results of the individually determined emetic thresholds for *i.v.* apomorphine in dogs are shown in Table I. The average latent period of vomiting was 1.5 min. These animals were subsequently injected intravenously with Dramamine or Benadryl to detect any inhibition of the emetic response to the threshold dose of *i.v.* apomorphine (see Table II.) Doses of 2 and 5 mg/kg of *i.v.* Dramamine caused no detectable inhibition of the vomiting response to apomorphine or increase in the latent period of emesis. Dramamine itself produced vomiting, ataxia and excitation in doses of 10 mg/kg. Nevertheless, dogs treated with this high dose of Dramamine again vomited following the threshold dose of apomorphine. With doses of 1 and 2.5 mg/kg *i.v.* Benadryl, there was no apparent difference in the incidence or the character of the apomorphine-induced emesis as compared with the controls.

The experiment of White and coworkers (5), on the protective effect of Dramamine against apomorphine-induced emesis, was repeated in 4 dogs. The control dog, untreated with Dramamine, vomited 2 min after the subcutaneous injection of 30 mg/kg apomorphine. Subsequently, the animal showed

TABLE III. Effect of Oral Dramamine and Benadryl on Latent Period of Vomiting Induced by Subcutaneous Apomorphine in Cats.*

Apomorphine control, min.	Apomorphine given 15 min. after		Apomorphine given 60 min. after	
	Dramamine, min.	Benadryl, min.	Dramamine, min.	Benadryl, min.
2	8	24	16	8
7	5	18	30	17
6	4	16	10	25
			15	7
Avg 5	6	19	18	14

* Dramamine and Benadryl: 75 mg, *per os*. Apomorphine: 65 mg, s.c.

hyperexcitability and continuous running, and it recovered only after several hours. The remaining 3 dogs received Dramamine, 2 mg/kg in 40 ml of water by stomach tube, 1 to 1.5 hours before the 30 mg/kg dose of apomorphine. Following the apomorphine, they vomited and showed the above-mentioned toxic reactions. No protective effect of Dramamine was demonstrated. We attempted to reproduce the experiments of Mitchell(8) who reported that Dramamine caused a greater inhibition of apomorphine-induced vomiting in cats than did Benadryl. The results obtained in 7 cats are shown in Table III. Apomorphine, 65 mg in 2.5 ml of water, was given subcutaneously 15 min after the oral administration of 75 mg Dramamine or Benadryl in 30 ml of water. The control untreated cats vomited after an average latent period of 5 min following the injection of apomorphine. Dramamine did not prevent emesis and there was no significant difference between the average latent periods in the control and the Dramamine-treated cats. Benadryl likewise did not prevent the vomiting. However, Benadryl did prolong the average latent period of emesis approximately 4-fold over the control value. Because 15 min might have been insufficient for adequate absorption from the gastrointestinal tract, another series of experiments was performed in which one hour was permitted to elapse between the oral administration of Dramamine or Benadryl and the injection of subcutaneous apomorphine. In spite of this precaution, no prevention of emesis resulted. However, Dramamine prolonged the latent period of emesis to approximately the same extent as did Benadryl. To rule out the disturbing factor of the development of tolerance to apomorphine, reported by Mitchell(8), some of the experimental cats were tested with apomorphine alone at the end of the investigation. These animals vomited after latent periods which approximated their original control values.

In order to determine the effects of the "anti-emetics" on the vomiting initiated by a different type of emetic stimulus, cats treated with *i.v.* Dramamine were tested with oral copper sulfate. It was first established that the dose of 20 mg of copper sulfate in 25 ml of water was effective in eliciting emesis in all of 14 normal fasted cats. Dramamine, 5 mg/kg, given intravenously 15 min prior to this oral dose of copper sulfate, failed to prevent vomiting in all of four cats tested. The average latent period of vomiting was 35 min, which compares favorably with control values.

Discussion. The advantages of determining the intravenous threshold emetic dose of apomorphine for each animal are as follows: Vomiting is elicited consistently with a reproducible latent period; development of tolerance is avoided; a minimal stimulus is provided; and the problem of sex difference in apomorphine susceptibility, claimed by Chen and Ensor(3) to occur with the subcutaneous route, is circumvented. Despite the use of this sensitive emetic test, no inhibition of apomorphine-induced emesis was obtained with either Dramamine or Benadryl.

Two possible sites of an anti-emetic action of Dramamine and Benadryl are a) the medullary emetic chemoreceptor trigger zone in the area postrema(9) and b) the vomiting center in the lateral reticular formation of the medulla. If the emetic effect of centrally-acting drugs, such as apomorphine and *i.v.* cardiac glycosides(10), is prevented by an anti-emetic agent without a concomitant reduction in re-

sponsivity to peripherally-acting emetics, such as oral copper sulfate(11), then the site of the anti-emetic action would be localized to the chemoreceptor trigger zone and/or its pathway to the emetic center. On the other hand, if both centrally- and peripherally-acting emetics become inactive after anti-emetic therapy, then a direct inhibitory action on the emetic center itself would be a sufficient explanation for this effect, although receptor sites and afferent pathways might be blocked as well. Unfortunately, the lack of anti-emetic activity of Dramamine and Benadryl in the present series of experiments makes localization of their site(s) of action impossible. However, if prolongation of the latent period of drug-induced vomiting can be considered to constitute a degree of protection, then some interpretation of the results becomes feasible. By the oral route Benadryl was found to be more effective than Dramamine in prolonging the latent period of vomiting in response to *s.c.* apomorphine in the cat, when 15 min were allowed for absorption from the gastrointestinal tract, but the two drugs were equally effective in prolonging the latent period when one hour was allowed for absorption. With regard to the emetic response to oral copper sulfate, no increase in the latent period was evident after *i.v.* Dramamine. On the basis of the above discussion, these findings would seem to imply that the anti-emetics studied may selectively depress the chemoreceptor trigger zone, but it must be re-emphasized that they merely prolonged the latent period without preventing the emetic response to apomorphine.

Summary. 1. Neither Dramamine (2, 5 and 10 mg/kg) nor Benadryl (1 and 2.5 mg/kg) administered intravenously was effective in preventing the emetic responses to threshold doses of intravenous apomorphine or in prolonging the latent periods of vomiting in 5 standardized dogs. 2. Other experiments were performed in the attempt to verify the reported protection afforded by Dramamine and Benadryl against apomorphine-induced emesis in dogs and cats. Although the latent period of emesis was prolonged in one of the experiments on cats, these drugs did not prevent vomiting.

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