Alteration of *In Vivo* Propulsive Intestinal Motility by Antihistaminic Drugs.* (18776)

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Studies on the effect of antihistaminic drugs on *in vivo* intestinal motility have made use of the following experimental preparations: Thiry-Vella loops(1), exteriorized loops of intestine(2) as described by Biebl(3) and by Douglas and Mann(4), intestines made "permanently opaque" to X-ray(5), and intestines left *in situ* after laparotomy(6-8). An indidirect approach was used by Erspamer and Paolini(9) who reported an effect of antihistaminic drugs on the rate of action of purgatives. Observations of propulsive intestinal motility, as such, have been made by measuring the rate of transport of a charcoal-acacia mixture through the gastrointestinal tract (10). Comparable investigations have been made in which carmine was used as a "marker" for the time periods between ingestion of a meal and defecation of the residue(11).

Most of the technics used to determine the effect of antihistaminic drugs on intestinal motility involve extensive preparative surgery in order to get an *in vivo* preparation which is both easily duplicatable and relatively normal physiologically. In order to avoid this preparative surgery, an attempt was made to investigate *in vivo*, the effect of antihistaminic drugs on only the propulsive aspect of intestinal motility, this being measured by observing the time from ingestion of carmine to its defecation. The studies, here presented, show the effect obtained with the use of the following 5 drugs: Diphenhydramine hydrochloride (Benadryl), tripelennamine hydrochloride (Pyribenzamine), thenylpyramine hydrochloride (Histadyl), phenazoline hydrochloride (Antistine), and phenindamine acid tartrate (Thephorin).

Experimental. Seventy-one male rats of 80-110 days of age were used, that had been obtained from the inbred Wistar stock colony of the Department of Biochemistry. All rats were put into individual wire nutrition cages and fasted for 24 hours prior to the feeding of the dye. The antihistaminic drug was administered by subcutaneous injections of equal size at 9 hours, 5 hours, and 30 minutes, respectively, prior to the time of feeding the dye. All drugs were given in terms of millimoles (mM) per kilo body weight per injection in slightly acid isotonic saline, the solutions having been made up fresh daily from the crystalline salt. The dye was fed as a dry colored checker (Purina Laboratory Chow) which had been prepared by soaking the checkers in an alkaline aqueous solution of carmine followed by room-temperature drying. Each rat was given 2 dyed checkers at the beginning of the feeding period and this

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TABLE I. Effect of Antihistaminic Drugs on Time from Ingestion of Carmine to its Defecation.

Date of exp.	No. of rats	Grp.	Drug	Dose, mM/kg per inj.	Time,* hr	Significance Groups compared	Significance "P"†
11-24	7	I	Saline	—	4.05 ± .45		
11-24	7	II	Benadryl	.16	5.25 ± 1.03	I,11-24::II,11-24	.01
12-11	5‡		No inj.	—	3.80 ± .48	II,11-24::II,12-11	.01
	7		(No inj.)	—	(3.15 ± 1.18)	(II,11-24::II,12-11)	(<.01)
-20	6§		Benadryl	.08	4.65 ± .60	II,12-11::II,12-20	<.05; >.02
11-26	7	III	Benadryl	.04	3.35 ± .67	I,11-24::III,11-26	.06
12-4	7		No inj.	—	4.20 ± .78	III,11-26::III,12-4	.05
-7	7		Benadryl	.12	4.30 ± .95	III,12-4::III,12-7	<.9 ; >.8
11-24	7	IV	Thephorin	.16	"too toxic to eat"		
12-11	7		No inj.	—	4.55 ± .77		
-20	7		Thephorin	.08	5.55 ± 1.08	IV,12-11::IV,12-20	<.1 ; >.05
11-26	7	V	Thephorin	.04	2.45 ± .70	I,11-24::V,11-26	<.01
12-4	7		No inj.	—	3.95 ± 1.04	V,11-26::V,12-4	<.01
-7	4‖		Thephorin	.12	3.80 ± .24	V,12-4::V,12-7	<.8 ; >.7
11-25	7	VI	Histadyl	.12	"too toxic to eat"		
12-11	7		No inj.	—	4.85 ± .70		
-20	7		Histadyl	.04	5.30 ± 1.06	VI,12-11::VI,12-20	<.4 ; >.3
11-25	7	VII	Antistine	.12	5.15 ± .69	I,11-24::VII,11-25	<.01
12-4	7		No inj.	—	4.65 ± .59	VII,11-25::VII,12-4	<.2 ; >.1
-7	7		Antistine	.04	4.20 ± .51	VII,12-4::VII,12-7	<.2 ; >.1
11-25	7	VIII	Pyribenzamine	.12	"too toxic to eat"		
12-11	5¶		No inj.	—	4.65 ± .29		
-20	5¶		Pyribenzamine	.04	4.15 ± 1.45	VIII,12-11::VIII,12-20	<.5 ; >.4
12-22	15	IX	No inj.	—	3.70 ± .55	I,11-24::IX,12-22	<.2 ; >.1
-26	15		" "	—	4.05 ± .74	IX,12-22::IX,12-26	<.2 ; >.1
-29	15		" "	—	3.60 ± .69	IX,12-22::IX,12-29	<1.0; >.9

* Means and std dev.

† "P" calculated by the t test of unpaired variates(12).

‡ Two rats were apparently still showing effects from previous Benadryl administration and not included in these values, but included in values in parentheses directly below.

§ Only 6 rats remaining in this group because one was sacrificed for reasons unrelated to exp.

‖ Only 4 rats in this exp. Remaining 3 were apparently "too toxic to eat."

¶ Only 5 rats remaining in this group because remaining 2 died of toxicity following first pyribenzamine administration.

amount of food was supplemented with undyed checkers after the first had been eaten. For all experiments, the injections were given during the daylight hours and the dye was fed at about 7:30 P.M. With such a schedule there were practically no environmental disturbances for the rats during the eating period and they could maintain their normal nocturnal eating habits. The room in which the rats were being observed was kept relatively dark after feeding of the dye. A clean paper towel was placed under each cage one hour after the initial feeding. Thereafter, inspections for carmine-colored feces were made at 15-minute intervals by using a small flashlight, so as to cause only a minimal unregulated environmental disturbance. Inasmuch as some of the drugs caused drowsiness and because an eating animal was essential for this test, the wire on each cage was scratched once, at the time of feces inspection, with a metal spatula in order to give a regulated awakening stimulus.

Results and discussion. The results are summarized in Table I. Benadryl in the dose of 0.16 mM produced an average *increase* in time of 1.20 hours (30%; $P = 0.01$) between the time of ingestion of carmine and its appearance in the feces. In a dose of 0.04 mM, Benadryl caused an average *decrease* in time of 0.7 hour (17%; $P = 0.06$). This reversal in type of activity by Benadryl, as produced by increased dosage, is comparable to that reported by Scudi, Reinhard, and Dreyer(7) who observed the intestine *in situ* and found thonzylamine hydrochloride

12. Freeman, H. A., *Industrial Statistics.* 1942, John Wiley and Sons, Inc., New York, p48.

(Neohetramine) to act as a stimulant in small doses and as an inhibitor in large doses. Similar effects have been observed(8) with prophenpyridamine (Inhiston).

The rats which received Thephorin in the dose of 0.16 mM failed to eat and seemed to show signs of toxicity after the last injection. However, the rats which received 0.04 mM of Thephorin showed an average *decrease* in time from ingestion of carmine to its defecation of 1.60 hours (40%; $P = <0.01$). This stimulation of motility is comparable to but somewhat greater than that seen after 0.04 mM of Benadryl.

Like the rats receiving 0.16 mM of Thephorin, the rats receiving Histadyl and Pyribenzamine in a dose of 0.12 mM, also failed to eat and were apparently poisoned by the drugs. Two of the 7 rats receiving 0.12 mM of Pyribenzamine died in less than 24 hours after the last injection. A dose of 0.04 mM of either Histadyl or Pyribenzamine failed to produce a significant effect.

Antistine when given in a dose of 0.12 mM produced an average *increase* in time of 1.05 hours (26%; $P = <0.01$). The Antistine, therefore, when given as 0.12 mM showed an inhibition of motility comparable to that seen when Benadryl was given in the larger dose of 0.16 mM. This comparison of Antistine and Benadryl is in agreement with the work of Erspamer and Paolini(9) who found Antistine to be a greater inhibitor of purgatives than Benadryl.

Inasmuch as the rat is relatively resistant to histamine(8) high doses of the antihistaminic drugs, approaching toxicity, were used in order to show the alterations in *in vivo* propulsive intestinal motilities as measured by observing the time from ingestion of carmine to its appearance in the feces. A comparable study in other species has not yet been made. However, both the data of this report and that of other work to which reference has been made, indicate that such a study should be made in order to see whether size of dose and chemical type of drug(13) should be taken into consideration when prescribing antihistaminic compounds.

Summary. 1. Antihistaminic drugs can affect the rate of *in vivo* propulsive intestinal motility as measured by observing the time between ingestion of carmine and its appearance in the feces. In comparable small doses Thephorin and Benadryl stimulate intestinal motility. 2. In larger doses, Antistine and Benadryl produce inhibition. This then shows a reversal in effect by Benadryl dependent on size of dose.

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Isolation of Coxsackie Viruses. Litter Differences Among Suckling Mice.* (18777)

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In planning a large scale study designed to throw light on the role of Coxsackie or C viruses in human disease by determining the frequency with which these agents may be demonstrated in specimens from various sources, an effort has been made to establish rigid technical criteria. It is common practice(1-4) to use one litter of suckling mice for each specimen being tested, although some investigators use two(5), and still others(6)

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