Gastric Ulcers Induced by Phenylephrine in Certain Pharmaceutical Compositions

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The incidence of gastric ulcers in mice was 100 per cent within 24 hours after a single oral sublethal dosage of an antihistamine-decongestant liquid pharmaceutical. Such ulcers persisted for more than 4 days. Investigation of the components of this and similar preparations indicated that phenylephrine was the primary ulcerogenic factor. The flavoring and sweetening agents, but not the antihistamines, significantly potentiated the ulcerating effect of phenylephrine. The results suggest that the composition of the base as well as the active agents in sympathomimetic amine-containing liquids may be important in eliminating the potential side effects of such preparations. The study also presents a reproducible and rapid method of ulcer induction for the investigation of antiulcer agents.

Acetylsalicylic acid, cortisone, histamine, cinchophen, and reserpine induced varying degrees of gastric ulceration in animals. Iodoacetamide fed to rats for up to 90 days produced chronic gastric ulceration without perforation or serious nutritional disturbances, suggesting a useful method in the studies of pathogenesis (1). Food reduction and drug-induced starvation caused gastrointestinal ulceration (2). Cutaneous necrosis resulted from intravenous infusion of norepinephrine in 61 human cases as reported by Close and Frackelton (3). Peirce and Polley (4) reported in two human cases that phenylephrine hydrochloride causes sloughing following intravenous infusion. No known reports of gastrointestinal ulceration are associated with the oral use of phenylephrine. Since mild gastrointestinal symptoms are occasionally observed with large doses, therapy with phenylephrine is recommended after meals (5).

Gastric ulceration, observed as a side effect of an antihistamine-sympathomimetic liquid preparation in an acute toxicity study, prompted further investigation, as presented in this report.

METHODS AND MATERIALS

Three liquid decongestant formulas containing a sympathomimetic and antihistamines were studied, as well as certain components, singularly and in combination. The drugs were administered either orally or subcutaneously in nonfasting Swiss mice (19–41 Gm.) and Wistar rats (198–369 Gm.). The oral dosage was usually 25 ml./Kg. Animals were sacrificed at 1 to 7 days after administering the drug. The per cent ulcer incidence was determined grossly. The degree of severity was expressed as the percentage of the pyloric stomach area found ulcerated.

The three basic formulas investigated contained the following active principles:

Formula A.—Each 5-ml. quantity contained 5 mg. of phenylephrine hydrochloride, 4.16 mg. of methapyrilene fumarate, 4.16 mg. of pyrilamine maleate, 4.16 mg. of pheniramine maleate, and 5% ethanol in a sweetened flavored base.

Formula B.—Each 5-ml. quantity contained 5 mg. of phenylephrine hydrochloride, 2.0 mg. of chlorprophenpyridamine maleate, 13.5 mg. of chloroform, 1.0 mg. of *l*-menthol, and 5% ethanol in a sweetened flavored base.

Formula C.—Each 5-ml. quantity contained 12.5 mg. of phenylpropanolamine hydrochloride, 6.25 mg. of pheniramine maleate, and 6.25 mg. of pyrilamine maleate in a sweetened flavored base.

RESULTS

Evaluation of the Active Constituents.—Gastric ulceration was induced by orally administering to mice 25 ml./Kg. of Formula A containing phenylephrine hydrochloride and three antihistamines as indicated in Table I. The 48-hour ulcer incidence ranging from 44.4 to 100% appeared to have a dose-response relationship. The ulcers, found only in the pyloric part of the stomach, consisted of multiple areas of epithelial erosion and hemorrhage. As much as 90% of the pyloric stomach area was eroded but without perforation. Hepatic hemorrhage and congestion and stimulation of the central nervous system were generally the associated side effects. The three antihistamines of Formula A were not ulcerogenic. Phenylephrine alone, given at four times the dosage as contained in Formula A, induced only one-half the incidence of gastric ulcers.

Formula B containing phenylephrine and one antihistamine produced 20% the incidence of gastric ulcers as equivalent dosages of Formula A. The addition of the three antihistamines of Formula A to Formula B did not increase the ulcer incidence. Formula C containing phenylpropanolamine and two antihistamines did not induce gastric ulceration.

Phenylephrine given orally to female rats starting at 100 mg./Kg. and terminating at 300 mg./Kg. per day for 3 days produced intestinal hyperemia, hepatic hemorrhage, and weight loss, but no ulcers as shown in Table II. One rat died following 100 mg./Kg. on the first day, but none died following 200 and 300 mg./Kg. on subsequent days, suggesting the development of drug tolerance. Gastric ulceration was produced in two male rats given 100 mg./Kg. of phenylephrine orally per day for 2 days. Epitaxis, rhinorrhea, and central nervous system depression were observed following the dose on the first day only. One rat died after the second dose.

As illustrated in Table III, combinations of phenyl-

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TABLE I.—INDUCTION OF GASTRIC ULCERS IN MICE 48 HOURS AFTER ORAL ADMINISTRATION OF VARIOUS PREPARATIONS

Prepn.	Mice, No.	Sex	Dosage, ml.(mg.)[a]/Kg.	Mortality, %	Incidence, %
Normal saline	10	M	25(25)	0	0
Formula A[b]	30	M	25(25)	0	100
Formula A	10	F	25(25)	30	100
Formula A	10	M	6.3(6.3)	10	44.4
Formula A	10	F	6.3(6.3)	0	50.0
Formula A-1[c]	5	M	25(25)	0	0
Formula B[d]	10	M	25(25)	0	20
Formula B-1[e]	5	M	25(25)	0	0
Formula C[f]	10	M	25(25)	0	0
Phenylephrine-2%	15	M	5(100)	26.7	45.5
Phenylephrine-2%	10	M	10(200)[g]	100	...
Phenylephrine-2%	5	F	5(100)	0	60

[a] Figure in parenthesis is the dosage of the sympathomimetic in mg./Kg. [b] Each 5-ml. quantity contains 5 mg. of phenylephrine hydrochloride, 4.16 mg. of methapyrilene fumarate, 4.16 mg. of pyrilamine maleate, 4.16 mg. of pheniramine maleate, and 5% ethanol in the Formula A base. [c] The antihistamines in aqueous solution as contained in Formula A. [d] Each 5-ml. quantity contains 5 mg. of phenylephrine hydrochloride, 2 mg. of chlorprophenpyridamine maleate, 13.5 mg. of chloroform, 1 mg. of *l*-menthol, and 5% ethanol in a sweetened flavored base. [e] The antihistamines as contained in Formula A added to Formula B. [f] Each 5-ml. quantity contains 12.5 mg. of phenylpropanolamine hydrochloride, 6.25 mg. of pheniramine maleate, and 6.25 mg. of pyrilamine maleate in a sweetened flavored base. [g] Given subcutaneously.

TABLE II.—TOXIC AND ULCEROGENIC EFFECTS OF 2% PHENYLEPHRINE HYDROCHLORIDE BY ORAL ADMINISTRATION IN WISTAR RATS (198–369 Gm.)

Time, Hr.	Rats, No.	Sex	Dosage, ml./Kg.	Remarks	Autopsy[a]
0	3	F	5(100 mg.)	One death after 2 hr. Lost 8 Gm. body weight.	Hyperemia of small intestine.
24	2	F	5(100 mg.)	Lost 8 Gm. body weight.	Autopsied one rat. No obvious pathological changes.
48	1	F	10(200 mg.)	No symptoms.	
72	1	F	15(300 mg.)	No symptoms.	No gross pathological changes except for hepatic hemorrhage.
0	3	M	5(100 mg.)	Epitaxis, rhinorrhea, C.N.S. depression persisting for 4–6 hr.	
24	3	M	5(100 mg.)	Symptoms as above. One death[b] occurred.	One rat with one pyloric stomach ulcer; one rat with three pyloric stomach ulcers.

[a] Sacrificing carried out 24 hours after the previous dosage. [b] Decomposition was too advanced for autopsy.

TABLE III.—INDUCTION OF GASTRIC ULCERS FOLLOWING ORAL ADMINISTRATION[a] IN MICE OF VARIOUS FORMULA A ACTIVE CONSTITUENTS

Prepn.	Mice, No.	Sex	Time of Autopsy, Hr.	Mortality, %	Ulcer Incidence, %
Normal Saline	5	F	48	0	0
Ph-Phen[b]	5	F	48	0	20
Ph-Meth[b]	5	F	48	20	0
Ph-Pyr[b]	5	F	48	20	0
Ph-Phen-Meth[b]	5	F	48	40	0
Ph-Phen-Pyr[b]	5	F	48	20	0
Ph-Meth-Pyr[b]	5	F	48	0	0
Normal Saline	5	M	24	0	0
Ph-Phen[c]	5	M	24	80	0
Ph-Meth[c]	5	M	24	100	...
Ph-Pyr[c]	5	M	24	80	100
Ph-Phen-Meth[c]	5	M	24	60	50
Ph-Phen-Pyr[c]	5	M	24	60	0
Ph-Meth-Pyr[c]	5	M	24	60	0
Formula A[d]	7	F	48	0	71.5
Formula A-2	7	F	48	0	100
Formula A-3	8	F	48	0	100

[a] All preparations were administered in 25 ml./Kg. dosages. [b] Ph, 0.10% phenylephrine hydrochloride; Phen, 0.25% pheniramine maleate; Meth, 0.25% methapyrilene fumarate; Pyr, 0.25% pyrilamine maleate. Two antihistamines in combination; each is 0.125%. [c] Same as *b*, except concentrations for phenylephrine and antihistamines are 2.67 times greater. [d] A, Each 5-ml. quantity contains 5 mg. of phenylephrine hydrochloride, 4.16 mg. of methapyrilene fumarate, 4.16 mg. of pyrilamine maleate, 4.16 mg. of pheniramine maleate, and 5% ethanol in Formula A base. A-2, 0.1% sodium pyrosulfite added as preservative. A-3, order of mixing altered.

ephrine with one or two antihistamines of Formula A in aqueous solution at 25 ml./Kg. orally induced ulcers in one group only. The over-all incidence of ulcers by such treatment was 3.3%. Increasing the concentration and dosage by 2.67 times increased the incidence of ulcers and mortality.

Adding a preservative or changing the order of mixing did not alter the ulcerogenic effect of Formula A.

The results suggested that some factor in the ulcerogenesis besides phenylephrine was indicated in Formula A.

Evaluation of the Vehicular Constituents.—As demonstrated in Table IV, the ulcerogenic action of phenylephrine in Formula A was potentiated by lime, ethanol, sucrose with glucose, sucrose with glucose and glycerin, and vanillin with glucose. When the ethanol and glycerin, sucrose, lime, and vanillin were deleted from Formula A, the ulcerogenic effects were eliminated. Substituting 2.5 mg. of phenylpropanolamine for 1.0 mg. of phenylephrine nearly eliminated the ulcerogenic effect of Formula A. The ulcer incidence was less than 7%, and with only one pinpoint size ulcer in each of two mice.

Figure 1 shows that the duration of gastric ulceration induced by 25 ml./Kg. of Formula A persists for more than 4 days. The peak in severity occurred at about 2 days.

TABLE IV.—INDUCTION OF GASTRIC ULCERS IN MICE BY VARIATIONS IN FORMULA A INERT CONSTITUENTS[a]

Formula[b]	Mice, No.	Sex	Mortality, %	Ulcer Incidence, %
A	15	M	0	100
A	15	F	20	100
A-I-Su	5	M	20	0
A-I-Gl	5	M	0	0
A-I-Gly	5	M	20	0
A-I-Van	5	M	20	0
A-I-Li	5	M	0	40
A-I-Et	5	M	0	20
A-I-Blue	5	M	0	0
A-I-Red	5	M	0	0
A-I-Su-Gl	5	M	0	80
A-I-Su-Gl-Gly	5	M	0	100
A-I-Gl-Red-Blue	5	M	60	0
A-I-Gl-Red-Blue	5	F	40	0
A-I-Gl-Red-Blue-Li/2-Van	5	M	0	20
A-I-Gl-Red-Blue-Li/2-Van	5	F	60	50
A-I-Gl-Red-Blue-Li/2-Cyc	5	M	20	50
A-I-2 Gl	5	F	0	80
A-C[c]	15	M	0	0
A-C	15	F	6.7	14.3[d]

[a] All preparations were orally administered in 25 ml./Kg. doses. Autopsy was performed 48 hours after oral dosage. [b] Formula A, each 5-ml. quantity contains 5 mg. of phenylephrine hydrochloride, 4.16 mg. of methapyrilene fumarate, 4.16 mg. of pyrilamine maleate, 4.16 mg. of pheniramine maleate, and 5% ethanol (Et) in a base of 50% sucrose (Su), 35% liquid glucose (Gl), 6.3% glycerin (Gly), 0.025% vanillin U.S.P. (Van), 1% lime flavor (Li), Blue, FD&C Dye No. 1 (Blue), and Red, FD&C Dye No. 2 (Red) in water. Cyc, cyclamate sodium. A-I, phenylephrine and the three antihistamines of Formula A in aqueous solution plus various vehicular agents. Li/2, one-half the amount of lime as contained in Formula A. 2 Gl, two times the amount of glucose as contained in Formula A. [c] A-C, substituting 2.5 mg. of phenylpropanolamine hydrochloride in Formula A for 1 mg. of phenylephrine hydrochloride. [d] One pinpoint size ulcer found in each of two mice only.

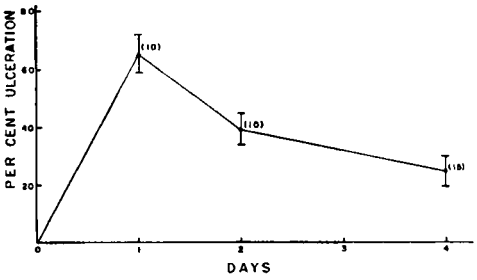

Fig. 1.—Pattern of gastric ulceration induced by oral administration of 25 ml./Kg. of Formula A in female mice. Per cent ulceration is based on the area of the pyloric stomach affected. I, mean and standard error. Number of animals in parentheses.

DISCUSSION

The mechanism of near lethal doses of phenylephrine, in producing gastric ulcers may be related to its effects on the autonomic nervous system, which include vasoconstriction of the gastric mucosa and constriction of the pyloric sphincter (6). Vasoconstriction results in ischemia and cellular anoxia and may lead to necrosis of the localized tissues as suggested by Close *et al.* (3). Ischemia and anoxia of the gastric mucosa, in the presence of retained gastric secretions, may be factors in the induction of gastric ulcers by phenylephrine in this study.

The possible role of the Formula A base in potentiating the ulcerogenic effects of phenylephrine is less obvious. Carbohydrates are reported to inhibit gastric motility, presumably by duodenal mucosa contact, which reflexly stimulates the release of the gastric inhibitory substance, enterogastrone (7). More specifically, Fenton (8) demonstrated that the volume of chyme emptied from the stomach was inversely proportional to the square root of the concentration of glucose orally fed to rats. This evidence suggests that the Formula A base inhibits gastric emptying and augments phenylephrine in producing a type of chemical pyloric ligation resulting in gastric ulcers, similar to the Shay rat (9).

The development of gastric ulcers, particularly in mice, is an acute toxic manifestation of phenylephrine and has questionable relationship to higher mammals. It is suggestive as a factor in the occasional mild gastrointestinal symptoms produced by large doses of such preparations.

The results indicate that the choice of apparent inert and active principles may be important in improving the gastrointestinal tolerance of sympathomimetic-antihistaminic liquid formulations.

The induction of gastric ulcers by phenylephrine in combination with high concentrations of certain sweetners, flavors, and solubilizing agents as contained in Formula A offers a rapid and reproducible method in the study of antiulcer drugs in mice, obviating thermocautery (10), chronic drug administration (1), and surgery, as with the Shay rat (9).

SUMMARY

Gastric ulcers were induced in mice by a single oral administration of liquid decongestant pharmaceutical.

Various liquid formulas containing a sympathomimetic drug and antihistamines, as well as different

combinations of active and inert principles, were evaluated for ulcerogenic effects in mice.

Phenylephrine hydrochloride was the initiating factor in the development of gastric ulcers.

Sucrose, glycerin, glucose, ethanol, lime, and vanillin potentiated phenylephrine-induced gastric ulcers in mice.

Phenylpropanolamine hydrochloride, similarly studied, produced little or no gastric toxicity.

These observations suggest that the composition of vehicle as well as the active principles may be important in reducing or eliminating the potential gastrointestinal side effects of sympathomimetic amine-containing liquid preparations.

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Effect of Chronic Poisoning by Emetine on Oxidative Process in Rat Heart I

Effects on Lipid Metabolism and Oxidative Phosphorylation

By GLENN D. APPELT* and HAROLD C. HEIM

Emetine at a concentration of $3 \times 10^{-3}M$ completely inhibited endogenous respiration of rat heart homogenates as well as the respiration in the presence of added butyrate or β-hydroxybutyrate. At a concentration of 10^{-4} *M*, the alkaloid elicited no effect. The inhibition observed was not specific for emetine, since quinine, at the same concentrations, was equally as effective in inhibiting respiration. Hearts from animals chronically poisoned by emetine, but not by quinine, showed impaired ability to oxidize these substrates. Chronic poisoning by emetine did not impair oxidative phosphorylation, nor did 10^{-3} *M* emetine added to mitochondria prepared from hearts of unpoisoned animals.

ABNORMALITIES in cardiac function following the use of emetine as an amebacide have been reported by numerous investigators. Ventricular fibrillation (1), diminished systolic force (2), and tachycardia (3) have been observed; other studies have shown that emetine may elicit a progressive cloudy swelling and fatty degeneration of the heart (4). Electrocardiographic changes have been induced by the drug in dogs and cats, evidenced by a widening of the initial P-R complex and by a frequently observed inversion of the T wave. These changes suggested a marked disturbance in energy utilization by the myocardium (5). Several studies have been conducted relative to the effects of emetine on cellular metabolism. It has been postulated that emetine may interfere with the enzyme systems which convert glycogen to contractile energy in the heart (6). Electrocardiographic alterations have been induced in the guinea pig by sublethal doses of the alkaloid, and these effects could not be prevented or abolished by the administration of diphosphopyridine nucleotide (7). It has also been shown that emetine evoked no effect on the synthesis of cocarboxylase by rat liver (8). The repeated administration of the alkaloid to young rats resulted in a reduction of food intake and marked inhibition of growth, findings which led to the suggestion that the drug caused nutritional and metabolic changes in certain tissues (10). A rapid depletion of liver glycogen has been reported to occur in young rats after a single administration of 0.1 to 0.2 mg. emetine/Kg. (11). Synthesis of glycogen by livers of emetine-poisoned rats was markedly depressed, and there also was observed a significant decrease in phosphorylase and aldolase activity in livers from the poisoned animals. Vitamin metabolism in emetine-poisoned rats has been studied; it was observed that the emetine-treated animals stored smaller amounts of thiamin and folic acid in the liver than did pair-fed controls. Poisoning by emetine did not alter metabolism of vitamin A, riboflavin, nicotinic acid, or biotin (12). The

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