Failure of antihistamine to protect against histamine-induced duodenal ulceration in the guinea-pig

SIR,—Previously it was demonstrated that the antihistamine drug, mepyramine maleate, reduces the incidence and greatly reduces the severity of gastric ulceration induced by histamine (Watt & Eagleton, 1964). We have since elaborated a method whereby histamine ulceration can be limited entirely to the duodenum (Eagleton & Watt, 1966). It was of interest therefore, to determine the effect of mepyramine on the production of such lesions in the guinea-pig.

Male albino guinea-pigs of 550 g were deprived of food for 12 hr before the start of the experiment and wore Perspex collars to prevent coprophagy. Water was supplied *ad lib.*

Duodenal ulceration was induced by the repeated intramuscular injection of histamine acid phosphate in aqueous solution (1 mg/ml). The injections (0·25 mg/kg) were given at 30 min intervals over a period of 3½ hr. Animals which received mepyramine maleate were given 10 mg/kg intramuscularly ½ hr before and again 2 hr after the first injection of histamine.

All animals were killed by a sharp blow on the head 4 hr after the first injection of histamine. The gastric juices were removed, their volumes measured, and total acid concentrations measured by titration against 0·04 N sodium hydroxide using phenolphthalein as indicator. The stomach and upper small intestine were distended with formol-saline and viewed by transillumination. The extent of damage was expressed in terms of the length of small intestine involved.

The incidence of histamine-induced duodenal ulceration in the control group and in the group treated with mepyramine maleate are shown in Table 1. In both groups the incidence of ulceration was 100%. There was no statistically significant difference in respect of the extent of involvement of the small intestine ($P>0·70$) or in relation to juice volume ($P>0·50$) and acid concentration ($P>0·30$) of the juices recovered at the end of the experiments.

TABLE 1. THE INCIDENCE AND EXTENT OF HISTAMINE-INDUCED DUODENAL ULCERATION IN MALE ADULT GUINEA-PIGS WITH AND WITHOUT ANTIHISTAMINE (2 × 10 MG/KG I.M.) (MEANS ± ONE S.D.)

	% with duodenal ulcers	Length of small intestine involved (cm)	Gastric juice at end of experiment	
			Volume (ml)	Total acid (m-equiv./litre)
With mepyramine (10 animals) ..	100	7·9 ± 1·8	5·6 ± 4·3	78·6 ± 14·7
Without mepyramine (10 animals) ..	100	8·7 ± 1·9	6·8 ± 4·8	68·8 ± 39·8

The failure of the antihistamine, mepyramine, to prevent histamine-induced duodenal ulceration is in striking contrast to the protective action of mepyramine against ulceration of the stomach induced by the same ulcerogenic agent. The dose of mepyramine used in this study was the same as that in the previous study in which protection was demonstrated against gastric ulceration caused by much larger doses of histamine (Watt & Eagleton, 1964). It is unlikely therefore that the failure to prevent duodenal lesions is due to inadequate dosage of antihistamine. It is of some interest that in the above experiments there was no suggestion that antihistamine materially altered the acidity or volume of gastric juice recovered at the end of the 4 hr period during which ulcers were forming.

The observation that an antihistamine drug interrupts the process of ulceration

in the stomach but not in the duodenum is interpreted as evidence that the mechanism whereby histamine causes gastric ulceration is different from that whereby histamine causes duodenal ulceration.

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A comparison of fluphenazine and chlorpromazine on critical flicker fusion frequency

SIR,—Besser, Duncan & Quilliam (1966) showed that chlorpromazine 25 and 50 mg depressed the auditory flutter fusion threshold at 90 and 180 min after administration, but neither 2 nor 4 mg of perphenazine altered it. It is also true that piperazine phenothiazine derivatives have less sedative effects than aliphatic derivatives.

Visual critical flicker frequency is a similar test of central nervous function. In a double-blind experiment, identical tablets of fluphenazine 1 mg, chlorpromazine 25 mg and a placebo were administered in random order to 6 young subjects, of either sex, in a Latin square design and with an interval between administrations of not less than 3 days. The critical flicker frequency was measured at 0, 2, 4 and 7 hr (Turner 1965, Smart & Turner, 1966) which involved exposing the subjects to intermittent light at 25 and 50 c/sec, for 1 min before measuring the critical flicker frequency.

Chlorpromazine produced a fall in the mean critical flicker frequency threshold between 0 and 4 hr compared with the placebo ($P < 0{\cdot}02$) but the change in threshold after fluphenazine was not significantly different from that after the placebo. Between 4 and 7 hr the threshold after chlorpromazine rose towards the resting level but was still depressed ($P < 0{\cdot}05$). The difference between the effects of chlorpromazine and the other two treatments was significant ($P < 0{\cdot}01$). None of the treatments influenced the adapting effect of light at 20 and 50 c/sec on the parameter, which is a stable phenomenon (Turner, Patterson & Smart, 1966).

It appears, therefore, that in this sensitive test of visual discrimination, the aliphatic phenothiazine derivitive chlorpromazine has a significant depressant action compared with the piperazine derivative fluphenazine.

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