Short Communication

Effect of aminoguanidine, chlorpromazine and NSD-1055 on gastric secretion and ulceration in the Shay rat

A. G. RADWAN* AND G. B. WEST†

Department of Pharmacology, School of Pharmacy, University of London, Brunswick Square, WC1

Both chlorpromazine and NSD-1055 (a non-steroidal anti-inflammatory drug) markedly lower the volume and acidity of gastric contents of rats subjected to pyloric ligation (Shay technique) and reduce the degree of ulceration in the stomach. On the other hand, aminoguanidine (an inhibitor of histaminase) has no effect on acid secretion or ulceration in these animals.

Shay, Komarov, Fels, Meranze, Gruenstein & Siplet (1945) found that gastric ulceration with increased gastric secretion was produced in rats within 16 h of pyloric ligation, the ulcers being predominantly in the thin fundic portion. Vagotomy afforded complete protection against this response (Harkins, 1947; Shay, Komarov & Gruenstein, 1949; Madden, Ramsburg & Hundley, 1951; Donald & Code, 1952) whilst marked inhibition was found after treatment with anticholinergic drugs (Shay, Gruenstein & Jamison, 1951; Antonsen, 1953).

Stimulation of gastric secretion has been postulated by Code (1956) to be a physiological function of histamine, the amine being the final common local chemostimulator of the parietal cells of the gastric mucosa. Later workers (Kahlson, Rosengren, Svahn & Thunberg, 1964; Code, 1965; Shore, 1965; Haverback, Stubrin & Dyce, 1965; Levine, 1965; Ivy & Bachrach, 1966) also considered that histamine plays a principal role in stimulating gastric secretion.

Using carboxyl labelled histidine, Radwan & West (1967) found that an enzyme in the thin fundic portion of rat stomach had some properties of specific histidine decarboxylase (Lovenberg, Weissbach & Udenfriend, 1962) whereas that in the less active but thicker pyloric portion resembled more the non-specific histidine decarboxylase which decarboxylates several aromatic amino-acids in addition to histidine. The *in vitro* activity of the enzyme in the fundic portion was later found by Radwan & West (1968a) to be markedly inhibited by aminoguanidine, an inhibitor of histaminase, but little changed by chlorpromazine; on the other hand, the activity of the enzyme in the pyloric portion was inhibited by chlorpromazine but only slightly changed by aminoguanidine. Further studies (Radwan & West, 1968b) showed that NSD–1055, a non-steroidal anti-inflammatory drug, inhibited both the specific and non-specific enzymes.

The present work was designed to investigate the action of high doses of aminoguanidine, chlorpromazine and NSD–1055 on gastric acid secretion and ulceration in Shay-operated rats, and to examine the finding of Antonsen (1953) that a correlation exists between gastric acidity and the extent of gastric ulceration in rats subjected to the Shay operation.

Methods.—Groups of twelve female Sprague-Dawley rats (120–150 g in weight) obtained from Fisons Pharmaceuticals Ltd., Holmes Chapel, had their pyloric sphincters ligated by the method of Shay *et al.* (1945), as modified by Pauls, Wick & Mackay (1947), Antonsen (1953) and Antonsen & Nielsen (1963). Briefly, they were placed in separate cages 24 h before the operation, during which time food was withdrawn but free access to an aqueous solution of 5% glucose and 0·4% sodium chloride was allowed. The operation was then carried out under light ether anaesthesia. A 15 mm long incision was made along the midline of the abdomen from the xyphoid process and a silk ligature was applied around the pyloric sphincter. After suturing the operation wound, 1 ml of a solution of a test compound or of 0·9% saline was injected intraperitoneally and the animals were returned to their cages, then without access to the glucose-sodium chloride solution.

Some of the rats died over the next 16 h, at which time those surviving were killed with chloroform. The stomachs of all animals were removed and cut along the greater curvature. The volumes of gastric contents were measured, and they were then centrifuged and titrated against 0·02 N–NaOH using phenolphthalein as indicator. The degree of gastric ulceration

* Present address: Department of Pharmacology, Faculty of Medicine, Al-Azhar University, Madinet Nassre, Cairo, U.A.R.

† Present address: North East London Polytechnic, Longbridge Road, Dagenham, Essex.

was determined by the naked eye using the system described by Pauls *et al.* (1947). Stomach ulcers were given scores from 1 to 4 according to their severity. When minor oesophageal ulcers were also present, 0·5 was added to the stomach score, and when these were severe 1·0 was added. The maximum score for each animal was therefore 5. The mean ulcer score for each group of rats was calculated and then multiplied by the percentage of ulcerated animals in the group to give the ulcer index.

Results.—Five rats out of a group of twelve Shay animals injected with 0·9% saline (that is, 42%) died within 16 h of the operation, showing signs of severe peritonitis and haemorrhage in the stomach. Ten animals in this group (that is, 83%) had gastric ulcers (mean ulcer score ±S.E. was 2·4±0·4) and all of these were found in the thin fundic portion. The mean volume ±S.E. of gastric contents in this group was 8·1±1·1 ml, with total acidity equivalent to 41·1±5·8 ml 0·02 N-NaOH. Aminoguanidine, an inhibitor of histaminase, one of the enzymes inactivating histamine, slightly increased the incidence of gastric ulceration and the volume and acidity of gastric contents; the mean ulcer score was not different from the control value (Table 1). On the other hand, chlorpromazine, an inhibitor of imidazole-N-methyltransferase, significantly reduced ($P<0·05$) both the extent of ulceration and the mortality rate of Shay rats. With considerably reduced ulcer scores in the few animals responding, the ulcer index was therefore considerably lowered, and the volume of gastric contents and its total acidity were also significantly reduced ($P<0·05$) (Table 1). NSD – 1055 (4-bromo-3-hydroxybenzyloxyamine) also significantly reduced ($P<0·05$) the severity and extent of ulceration although the volume and total acidity of the gastric contents were only slightly decreased (Table 1).

Discussion.—In the present study chlorpromazine exerted a powerful protective action against increased gastric secretion and gastric ulceration and a clinical trial in the treatment of human gastric ulcers is worthy of consideration. The drug has been in use in medicine in the treatment of psychotic diseases for a long time and large dose schedules have been used. Chlorpromazine inhibits imidazole-N-methyltransferase (Brown, Tomchick & Axelrod, 1959; Merril, Snyder & Bradley, 1966) yet this enzyme is lacking in rat stomach. Chlorpromazine also markedly inhibits the histidine decarboxylase activity in the pyloric portion and has little action on the enzyme in the fundic area, yet ulceration predominates in the fundic portion. It is possible therefore that its beneficial effect in the present experiments results from another action such as that on the central nervous system (the depressant action as used in human psychotic cases) which thereby produces an antiemetic effect and protection from ulceration (Borison & Wang, 1953).

Aminoguanidine inhibits histaminase and to some extent the histidine decarboxylase activity *in vitro* of the rat stomach. The net result of these two actions of aminoguanidine will depend on the relative strength of each and as they are antagonistic to each other circumstances may be such (as in the present experiments) that the compound has no significant effect on gastric secretion or on ulceration in Shay rats. Amure & Ginsburg (1964) found that aminoguanidine only increased gastric acid secretion in rats when injected together with histamine, a treatment which disturbed the balance between formation and destruction of the amine.

NSD–1055 is a potent inhibitor of both the specific and non-specific histidine decarboxylases and probably exerts its protective action in the Shay rat by reducing the activity of the specific enzyme in the thin fundic portion of the stomach

TABLE 1. *Effect of different substances on gastric secretion and ulceration in Shay rats*

	Saline control	Aminoguanidine 50 mg/kg	NSD-1055 200 mg/kg	Chlorpromazine 20 mg/kg
Gastric contents				
(a) Volume (ml)	8·1±1·1	9·8±1·2	6·0±0·8	2·0±0·4
(b) Acidity (ml 0·2N NaOH)	41·3±5·8	52·4±6·3	30·5±5·1	10·7±0·9
% Mortality	42	55	17	9
% Ulceration	83	91	33	28
Mean ulcer score	2·4±0·4	2·5±0·4	0·9±0·3	0·2±0·1
	199	228	30	6

(where the ulcers predominate) and thereby reducing the amount of histamine formed in that region. It is possible that inhibition of the non-specific enzyme in the thick pyloric portion also contributes to the protective action of this compound, as it may do in the case of chlorpromazine.

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