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THE EFFECT OF PENTAGASTRIN (I.C.I. 50, 123) ON PEPTIC SECRETION IN MAN

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SUMMARY

1. We have studied the peptic responses of the intact human stomach to stimulation by doses of pentagastrin which elicit a maximal acid response.

2. In twelve patients an intramuscular injection of pentagastrin (6 μg/kg) was followed by a prompt increase in acid output which attained a peak value eight times higher than the basal value in the period 15–30 min after stimulation. The pattern of the peptic response was similar, but the peak output of pepsin was only three times the output in unstimulated juice.

3. In ten subjects the acid and peptic responses to I.V. infusion of pentagastrin (1·2 μg/kg per hr) were studied using a gastric perfusion technique with ^{14}C-labelled polyethylene glycol as non-absorbable marker. In seven of these ten subjects the pH of duodenal contents exceeded 6, and less than 0·5 m-mole HCl per 15 min entered the duodenum throughout the tests. In this subgroup pentagastrin evoked a strong acid response but no peptic response.

4. In three subjects the pH of duodenal juice was less than 5·5 at times when more than 1 m-mole HCl per 15 min entered the duodenum. The acid response to pentagastrin differed considerably in the three subjects, but in each individual the output of pepsin increased each time an excess of HCl entered the duodenum.

5. Since pentagastrin infused in a dose which maximally stimulates acid did not significantly increase the output of pepsin provided no HCl entered the duodenum we conclude that pentagastrin does not stimulate the secretion of pepsin in man. The transient insignificant peptic response to pentagastrin infusions, and the small but significant response to bolus injections of pentagastrin, can be explained as a wash-out phenomenon.

INTRODUCTION

In anaesthetized cats, in which the pylorus was occluded to prevent the release by HCl of a peptic stimulant from the duodenal mucosa, intravenous infusions of caerulein (Braganza, Gibbs & Howat, 1975), gastrin II and pentagastrin (Beswick, Braganza & Howat, 1978, 1979), in doses which stimulated acid secretion submaximally and maximally, did not stimulate the secretion of pepsin. Comparable studies in man are technically difficult since complete but reversible pyloric occlusion is not feasible. In this study we have attempted an alternative approach to the

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problem, and examined the peptic responses in relation to the load of HCl which inadvertently enters the duodenum during infusions of pentagastrin in man.

METHODS

Pentagastrin injection. In a pilot study gastric secretion was analysed in patients with endoscopically proven duodenal ulceration who received standard pentagastrin tests to assess the parietal cell mass (Multicentre Study, 1967; Makhlouf, McManus & Card, 1966; Wormsely, Mahoney & Ng, 1966). After an overnight fast a nasogastric radio-opaque tube was passed and sited fluoroscopically. The stomach was aspirated by an intermittent suction pump at a negative

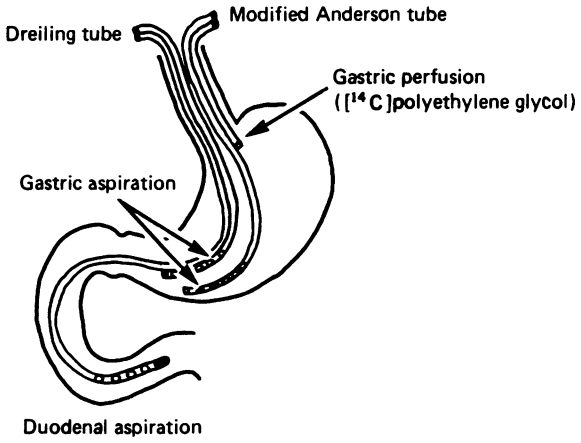

Fig. 1. Arrangement of tubes for quantitative pentagastrin infusion tests. Pentagastrin (6 μg/kg I.M., 1·2 μg/kg per hr I.V.) to elicit maximal acid response.

pressure of 25–30 cm Hg. Saliva was aspirated throughout. Gastric contents collected in the first 30 min were discarded. Thereafter gastric juice was aspirated at 15 min intervals for 1 hr before and 1 hr after an intramuscular (I.M.) injection of pentagastrin (I.C.I. 50, 123; 6 μg/kg).

Pentagastrin infusion. Five patients with antral or duodenal ulceration confirmed endoscopically (normal mucosa in the fundus and body of stomach) and five healthy volunteers were intubated as shown in Fig. 1. The tip of the Dreiling tube was adjusted fluoroscopically to lie at the ligament of Treitz. The modified Anderson's tube was sited so that the aspiration pores lay in the most dependent part of the stomach with the infusion site in the gastric fundus. Thirty minutes after intubation, constant perfusion of the stomach at 1·5–2 ml. per min with 5 mM-HCl in physiological saline containing 2·5 μc of ^{14}C-labelled polyethylene glycol (New England Nuclear Co.) was started, and continued for the duration of the test. Gastric juice was collected through the Anderson tube and the gastric pores of the Dreiling tube at a negative pressure of 25 cm Hg. Duodenal juice was aspirated separately through the duodenal portion of the Dreiling tube at a negative pressure of 5–10 cm Hg. Specimens were pooled into 15 min fractions for 60 min before and during a 60 min I.V. infusion of pentagastrin (1·2 μg/kg per hr).

Chemical methods. The volume of each gastric and duodenal sample was recorded to the nearest 0·5 ml., the pH measured, and the concentration of ^{14}C estimated by liquid scintillation counting. The concentration of HCl was determined by titration to pH 7 against sodium hydroxide in an automatic titrimeter, and pepsin by the method of Hunt (1948).

Analytical methods. The total amount of ^{14}C recovered in each experiment was calculated from the volumes and concentrations of ^{14}C in successive collections of gastric and duodenal juice. The volume of gastric juice which entered the duodenum each 15 min was estimated by dividing the amount of ^{14}C in each duodenal sample by the concentration of ^{14}C in each respective gastric sample. The amount of acid which entered the duodenum in successive periods could then be

assessed. Differences in the mean outputs of acid and pepsin in the four 15 min periods after stimulation compared to the respective outputs in the 15 min immediately preceding stimulation were assessed by paired t tests. A result was considered significant when $P < 0{\cdot}05$ (two-tailed tests).

RESULTS

Pentagastrin injection. Of the forty tests performed, only twelve were considered suitable for inclusion in the study. Tests were discarded if unsatisfactory technically (test terminated prematurely, patient swallowing saliva) or if the concentration of

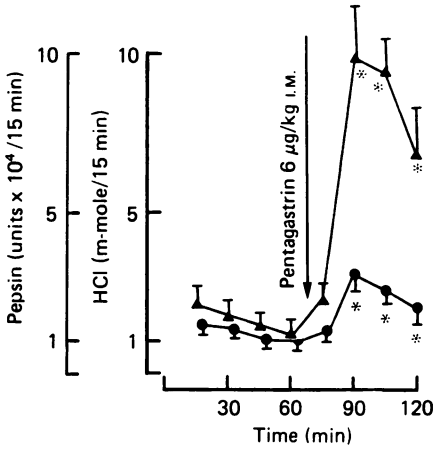

Fig. 2. Outputs of acid (▲) and pepsin (●) in response to I.M. injection of pentagastrin (6 μg/kg). Points are means ± S.E. of means of twelve studies. *, $P < 0{\cdot}05$.

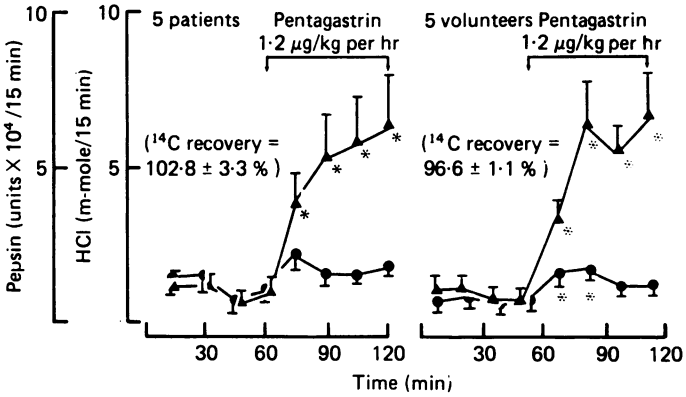

Fig. 3. Comparison of acid and peptic responses in five patients and five volunteers. Points are means ± S.E. of means of five studies in each subgroup. ▲, HCl; ●, pepsin; *, $P < 0{\cdot}05$.

chloride in any of the eight gastric samples was less than 100 m-mole/l., since contamination of gastric juice by saliva or duodenal juice may then be inferred (Hunt, 1951; Ihre, 1938).

The acid and peptic responses to i.m. injection of pentagastrin (6 μg/kg) are shown in Fig. 2. The peak output of HCl, approximately eight times higher than the basal value, occurred in the period 15–30 min after the injection and the output of HCl

remained significantly increased for the duration of the test. The pattern of the peptic response was similar but the peak peptic output was only three times the basal value (Fig. 2).

Pentagastrin infusion. Ten subjects were studied, of whom five were healthy volunteers and five were patients with active duodenal ulceration. In the group as a whole the total recovery of ^{14}C (amount from the stomach plus that recovered from the duodenum) was $99{\cdot}7 \pm 1{\cdot}9\%$ of the amount of ^{14}C infused (mean ± S.E. of

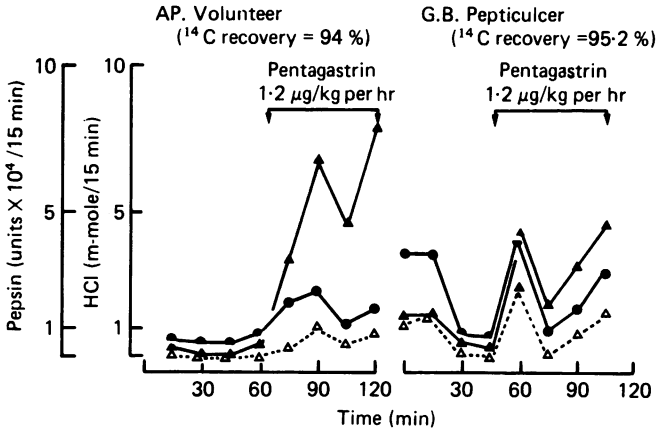

Fig. 4. Outputs of acid and pepsin in a pateint G.B.; and volunteer A.P. in whom at some stage 1 m-mole HCl per 15 min entered the duodenum. ●, Pepsin; ▲, HCl; △, HCl in duodenum.

mean in ten experiments). The pH of gastric contents was less than 4 throughout each test. No formal assessment of reflux of duodenal contents into the stomach was possible but the concentration of bilirubin in gastric contents was less than 0·5 mg/dl. in nine of the ten subjects. In a patient with an acute peptic ulcer (G.B. in Fig. 5) the concentration of bilirubin was 3 mg/dl. or less during the test but gastric pH remained < 4.

The pattern and magnitude of the acid responses of the volunteers and the patients were similar (Fig. 3). In each subgroup the outputs of HCl in the second, third and fourth periods after stimulation did not differ from one another and these values were approximately six times higher than the output of HCl in the period preceding stimulation. In the patients no peptic response was detectable. In the volunteers the output of pepsin increased in the first 30 min after stimulation (paired *t* tests) to attain values only twice as high as in basal juice.

Further scrutiny revealed that the pH in the duodenum exceeded 6 throughout the tests in seven (three volunteers and four patients) of the ten subjects studied. In these, less than 0·5 m-mole HCl per 15 min entered the duodenum. A transient increase in peptic output occurred in the first two periods after the start of the pentagastrin infusion but later the output of pepsin decreased towards the basal value ($0{\cdot}05 < P < 0{\cdot}1$; $0{\cdot}05 < P < 0{\cdot}1$; $0{\cdot}3 P < 0{\cdot}4$; $0{\cdot}3 < P < 0{\cdot}4$ in successive periods after stimulation).

In three subjects, a patient with peptic ulcer (G.B.) and two volunteers (A.P.; A.S.) duodenal pH was less than 5·5 at times when more than 1 m-mole HCl per

15 min entered the duodenum (Figs. 4 and 5). The magnitude of the acid response to pentagastrin differed considerably in these three subjects, while the peculiar fall off in acid output in the third period of stimulation in A.P., and in the second period of stimulation in G.B., was probably due to loss of acid into the jejunum since the total recovery of ^{14}C in these two individuals was less than in the other subjects studied.

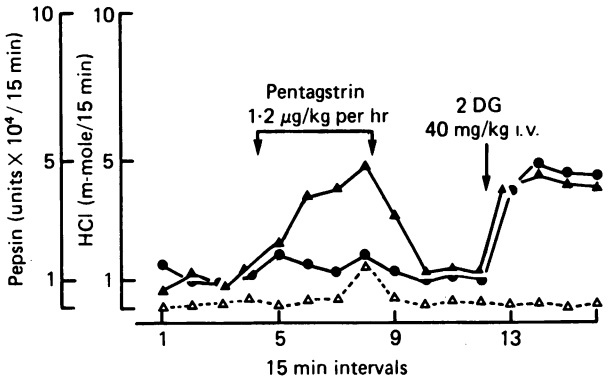

Fig. 5. Acid and peptic responses of volunteer A.S. who was given (2 DG, 2-deoxyglucose 40 mg/kg, I.V.) 60 min after the infusion of pentagastrin. ●, Pepsin; ▲, HCl; △, HCl in duodenum. ^{14}C recovery 98%.

However, in each subject the magnitude and the pattern of the peptic response was clearly linked to the amount of acid which inadvertently escaped into the duodenum, whether in the control periods or during stimulation with pentagastrin (Figs. 4 and 5). Volunteer A.S. (Fig. 5) received an I.V. injection of 2 deoxyglucose (2 DG; 40 mg/kg) an hour after pentagastrin, by which time gastric secretion had returned to basal values. The outputs of both acid and pepsin increased within 15 min of stimulation by 2 DG, the proportional elevation of each was similar and the secretion of each component was sustained during the next hour.

DISCUSSION

In recent years the synthetic gastrin-like pentapeptide pentagastrin has replaced histamine for routine clinical testing of parietal cell function in man. The effect of pentagastrin on the function of the chief cell in man has not however been clearly established.

The peptic responses to *single subcutaneous or intramuscular injections* of various acid secretagogues given in doses known to evoke comparable maximal flow rates of gastric acid have been compared in three studies, with discrepant results. Jepson, Duthie, Fawcett, Gumpert, Johnston, Lari & Wormsley (1968) considered histamine 40 μg/kg, pentagastrin 6 μg/kg, tetragastrin 10 and 20 μg/kg and gastrin I 2 and 4 μg/kg to be equipotent stimulants of pepsin; Makhlouf, McManus & Card (1966, 1967) concluded that pentagastrin 6 μg/kg, and gastrin II 1 μg/kg produced smaller peptic outputs than histamine 40 μg/kg; while Køster, Faber & Rødbro (1968) could detect no significant increase in peptic secretion over basal values when tetragastrin 20 μg/kg or histamine 40 μg/kg were given.

When pentastrin *was infused intravenously in doses ranging from* 0·006–6 μg/kg *per hr* in the study of Wormsley *et al.* (1966) the output of pepsin increased to a peak value within 20 min of stimulation and then decreased to a steady level amounting to twice the basal value. The initial spurt was attributed to 'washing-out' of preformed pepsin since it did not depend on the dose of pentagastrin, and changing the dose while the stomach secreted evoked an increase in peptic output only commensurate with the increase in acid. Aubrey (1970) and others (Aubrey & Forrest, 1970*a*, *b*; Cohen, Debas, Holubitsky & Harrison, 1971) concurred, and concluded that since pentagastrin produced a sustained twofold increase in peptic output compared to the value in unstimulated juice, it is a true stimulant of the chief cells. By contrast Berstad & Petersen (1971*b*) could not detect any clear cut dose–response relationship between graded doses of pentagastrin and peptic output, since the dose–response curve levelled off at 0·2 μg/kg per hr without evidence of pepsin inhibition by the higher doses. Accordingly they believed that pentagastrin is a poorer stimulant of pepsin than is histamine in man, and moreover, that pentagastrin does not provide the true maximal capacity of the human stomach to produce pepsin. In a later study from the same centre (Roland, Berstad & Liavåg, 1974) the highest peptic output in response to pentagastrin occurred when 1·5 μg/kg per hr was given, while a higher dose of 15 μg/kg per hr appeared to inhibit peptic secretion.

The discrepancies cited above are understandable when one considers the many problems inherent in the study of peptic secretion in man, namely, (*a*) the continuous interprandial secretion of pepsin (Ihre, 1938; Janowitz & Hollander, 1952; Hirschowitz, London & Pollard, 1957; Hirschowitz, 1961) which affects the basal value considerably, (*b*) the variable vagal influence which is difficult to eliminate, (*c*) the escape of gastric acid (Petersen & Berstad, 1973) which might release a peptic stimulant from the duodenal mucosa (Friedman, Pincus, Thomas & Rehfuss, 1944; Brooks, Isenberg & Grossman, 1969) and (*d*) contamination of gastric contents by regurgitated duodenal juice, or swallowed saliva (Ihre, 1938; Hunt, 1951) which would neutralize acid and inactivate pepsin (Berstad, 1971).

In an attempt to surmount some of these obstacles we deliberately employed a long basal period of 90 min (discarding juice in the first 30 min) to diminish peptic secretion due both to vagal stimulation, and to the passage of the gastroduodenal tube (Berstad & Petersen, 1971*a*). Aspiration from two separate sites within the stomach facilitated the collection of gastric contents, while the completeness of collection, and escape of HCl into the duodenum could be assessed by the gastric marker technique. The doses of pentagastrin used, 6 μg/kg by I.M. injection (Multicentre Pilot Study, 1967; Johnston & Jepson, 1967), 1·2 μg/kg per hr by continuous I.V. infusion (Mason, Giles & Clark, 1969) were selected to ensure a maximal stimulation of HCl.

In our study I.V. infusion of pentagastrin at 1·2 μg/kg per hr produced the expected acid response but no peptic response, provided less than 0·5 m-mole HCl per 15 min entered the duodenum. This behaviour contrasts sharply with the peptic response to vagal stimulation by 2 DG (Fig. 5) when a sustained increase in peptic secretion was apparent. It is thus likely that the peptic response to I.M. injection of pentagastrin (Fig. 2) is simply a wash-out phenomenon, and not due to stimulation of the chief cells.

That acidification of the duodenum leads to an increase in peptic output was established by the work of Friedman *et al.* (1944) and of Nakajima & Magee (1970) in dogs. In man, perfusion of the duodenum with 100 mM-HCl at 400 ml./hr (10 m-mole HCl per 15 min) produced a sustained increase in peptic output (Brooks *et al.* 1969) but the effects of perfusing smaller amounts of HCl, such as encountered in our study (Figs. 4 and 5) has not so far been documented. The precise mechanism of peptic response to duodenal acidification remains to be elucidated.

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