Gastrin sensitivity in duodenal ulcer

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SUMMARY The sensitivity to pentagastrin measured as D_{50C} , the dose required for half maximal acid output (MAO) corrected for basal acid output, in 200 patients with active duodenal ulcer was significantly ($p < 0.001$) higher than that in 36 age- and sex-matched controls, and was above the normal limit in 27% of the patients. The distribution of D_{50C} was significantly different between early onset and late onset patients, defined as patients whose ulcer symptoms started at respectively age ≤ 30 years and age > 30 years. Among patients whose MAO/kg body weight was within 2 SD of the normal mean as established previously in 100 normal subjects, gastrin sensitivity was significantly greater in late onset than in early onset patients, and in those who were positive than in those who were negative for familial ulcer dyspepsia. Among patients with abnormally large MAO, the reverse was true, gastrin sensitivity being greater in early rather than in late onset patients, and in patients negative rather than in those positive for familial ulcer dyspepsia. These findings suggest that (1) gastrin hypersensitivity is a distinct physiological abnormality in duodenal ulcer, (2) the increased gastrin sensitivity in some patients with normal MAO has a genetic basis but the lateness in onset of their disease also suggests an environmental origin, and (3) the increased gastrin sensitivity in some patients with abnormally large MAO is related to environmental factors encountered early in life.

Isenberg *et al* showed that the pentagastrin dose response curves of patient with duodenal ulcer were distinctly shifted to the left of those of the normal subjects, and that the mean D_{50} – that is, dose required for half-maximal acid output was significantly lower in the ulcer patients than in the controls, indicating that patients with duodenal ulcer as a group were more sensitive to pentagastrin.¹ The results were subsequently confirmed by some workers^{2,3} but not by others.^{4,5} Much evidence⁶ has accumulated from epidemiological, clinical, genetic, and pathophysiological studies to support the concept that duodenal ulcer is a heterogeneous condition.^{7,8} This may partly explain the apparent controversy of the pentagastrin sensitivity studies, particularly because the number of patients in these studies was small and may not represent the patients with duodenal ulcer at large. As Grossman⁹ pointed out, it is time that we should not only ask which physiological mechanism is abnormal but also how often it is abnormal in a given population of patients with duodenal ulcer?

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The present study examined 200 patients with duodenal ulcer to define (1) how often hypersensitivity to pentagastrin occurs, and (2) its relationship to known subgroups of duodenal ulcer: early onset and late onset patients,¹⁰⁻¹² patients with and without a history of familial ulcer dyspepsia,^{10,13} patients with normal and those with abnormally large maximal acid output.¹⁴⁻¹⁷

Methods

PATIENTS AND CONTROLS

A series of 234 unselected patients with endoscopically proven active duodenal ulcer were studied. They did not have any concomitant medical illness or previous gastric surgery. They did not receive anticholinergics or H_2 -receptor antagonists in the week before the study. Two hundred were included for final analyses because they satisfied the criteria that the calculated maximal acid output (c) obtained from the pentagastrin dose-response curve (*vide infra*) and the observed maximal acid output (o) differed by $< 20\%$ ($|c - o|/c \times 100 < 20$) and that the correlation coefficient of the dose-response curve was > 0.5 . There were 148 men with a mean

age of 36.9 years (range 13–75 years) and 52 women with a mean age of 43.4 years (range 12–80 years). Using the same criteria, 38 of 50 subjects were used as controls. These included healthy volunteers and carefully selected patients with minor, non-specific indigestion who were otherwise healthy and who had normal macroscopic and microscopic findings at upper gastrointestinal endoscopy with random biopsies, two from duodenum, four from antrum, and four from body and fundus of the stomach. There were 23 men with a mean age of 38.5 years (range 17–70 years) and 15 women with a mean age of 43.1 years (range 21–69 years). Informed consent was obtained in all subjects. The protocol for the pentagastrin dose response studies was approved by the ethical committee, University of Hong Kong.

The patients with duodenal ulcer were divided into early onset and late onset subgroups according to whether their age of onset of ulcer symptoms started at ≤ 30 years, or > 30 years respectively. The cut off point at age 30 years was based on previous studies indicating that early onset patients differed from late onset patients, particularly in being more familial, and having the same blood group distribution as the general population instead of blood group O predominance, as in late onset patients.^{10–12} Patients were also grouped as having positive or negative family history of ulcer dyspepsia. Familial dyspepsia was considered present when the patient indicated that ulcer dyspepsia, gastrointestinal bleeding, perforation, or gastric surgery, or a combination of any or all, had occurred in a first degree relative. They were also classified as normosecretors and hypersecretors depending on whether their pentagastrin stimulated maximal acid output per kg total body weight (MAO/kg) were within or > 2 SD of the mean MAO/kg of normal as established previously in 100 normal Chinese subjects.¹⁸ Mean MAO and mean MAO/kg in these normal subjects were 12.7 ± 5.8 mmol/h and 0.25 ± 0.10 mmol/h/kg respectively.

PENTAGASTRIN DOSE-RESPONSE STUDIES

The procedure had been described in detail previously.¹⁹ After an overnight fast, gastric acid output in response to infusions of pentagastrin administered as follows was measured: 0 (0.15M saline, 1.5 mmol/h), 93.8 375, 1500, and 6000 ng/kg/h. Each dose of pentagastrin was infused for 30 minutes into a forearm vein by a syringe infusion pump (Harvard Apparatus Co, Inc, Millis, Maso). The final dose, 600 ng/kg/h, was infused over 60 minutes. Gastric juice was collected at 15 minute intervals. The acid output during saline infusion was the basal acid output and that during infusion of 600 ng/kg/h pentagastrin was the observed MAO. The

dose required for half-maximal response (D_{50}) was estimated by linear regression analysis according to the equation: response = calculated maximal response – D_{50} (response/dose), which gave D_{50} as the negative slope. The D_{50} corrected for basal acid output (D_{50C}) was calculated according to the equation: $D_{50C} = D_{50} [1 - \text{basal acid output} / (\text{calculated MAO} + \text{basal acid output})]$. The D_{50C} was taken to represent the sensitivity of the parietal cells in response to pentagastrin stimulation. The methodologies, validation experiments, and calculations were detailed previously.^{1,3}

D_{50C} of an individual patient was regarded as abnormally low if the value was below 50 ng/kg/h (the lowest obtained in the controls was 55 ng/kg/h).

STATISTICAL ANALYSIS

Logarithmic transformation was done on all D_{50C} values before the groups were compared for differences in variance using analysis of variance and for differences in means using unpaired *t* test.²⁰ When either of these tests gave a two-tail *p* value < 0.05 , a significant difference between groups was considered to be present. The mean D_{50C} values described in the results section are the conventional arithmetic means and SE, and are presented so that readers can compare these with previously reported values in the literature. Chi-square test with Yate's correction was used to compare proportions.

Results

PATIENTS WITH DUODENAL ULCER AND THEIR VARIOUS SUBGROUPS COMPARED WITH CONTROLS
The basal acid output and acid output following different doses of pentagastrin in patients with duodenal ulcer and controls were shown in the Figure. Significant differences in basal and stimulated acid output were obtained between the two groups.

Compared with controls, mean D_{50C} was significantly lower in patients with duodenal ulcer whether taken wholly or subdivided into early and late onset, normosecreting and hypersecreting, familial ulcer dyspepsia positive and negative subgroups (Table 1). When the patients were broken down into further subgroups (Tables 2 and 3), this remained true except for the following: familial ulcer dyspepsia negative normosecretors; familial ulcer dyspepsia negative, late onset subjects; late onset hypersecretors, irrespective of whether or not they were positive for familial ulcer dyspepsia.

A significant difference in variance but not in means was found between early and late onset subgroups, suggesting a difference in distribution

Figure Acid output, basal acid in response to graded doses of pentagastrin, of 200 patients with duodenal ulcer and 38 controls.

between these subgroups. No significance in variance or means, however, between normosecretors and hypersecretors, nor between familial ulcer dyspepsia positive and negative subjects could be observed (Table 1).

EARLY AND LATE ONSET SUBGROUPS

Because of the significant difference in the distribution of D_{50C} between early and late onset patients, these were further analysed according to their secretory capacity and familialness for ulcer dyspepsia (Tables 2 and 3). Among normosecretors, late onset patients had significantly lower mean D_{50C} than early onset patients (Table 2) and this remained true irrespective of whether they were positive or negative for familial ulcer dyspepsia (Table 3). Among hypersecretors, however, the reverse was true, with early onset patients having

significantly lower mean D_{50C} than late onset patients (Table 2), and this remained apparent after patients were further divided into familial ulcer dyspepsia positive and negative subgroups. Among patients with positive familial ulcer dyspepsia, a significant difference was likewise observed between early and late onset patients, but such a difference was not present in patients with negative familial ulcer dyspepsia (Table 2).

FAMILIAL ULCER DYSPEPSIA POSITIVE AND NEGATIVE SUBGROUPS

As a group no significant difference occurred between these patients (Table 1), and this remained true irrespective of whether they had early or late onset disease (Table 2). Among normosecretors, patients who were positive for familial ulcer dyspepsia had significantly lower mean D_{50C} than those who were not, and this trend was still apparent when the normosecretors were subdivided into early and late onset subjects, but the differences were not statistically significant. Among hypersecretors, however, the opposite was true, patients who were negative for familial ulcer dyspepsia having significantly lower D_{50C} than those who were positive, but this trend was lost when patients were subdivided into early and late onset subjects.

NORMOSECRETORS AND HYPERSECRETORS

Although as a group normosecretors – that is, patients with normal MAO, and hypersecretors – that is, patients with abnormally high MAO, did not differ in their D_{50C} , late onset normosecretors had significantly lower mean D_{50C} than late onset hypersecretors. No significant difference, however, was present between early onset normosecretors and early onset hypersecretors (Table 2). Likewise, no difference could be detected between normosecretors and hypersecretors irrespective of whether they were positive or negative for familial ulcer dyspepsia (Table 3). This remained true when patients were further subdivided into early and late onset subgroups except that among late onset

Table 1 D_{50C} (ng/kg/h) in duodenal ulcer (DU) and its major subgroups and in normal controls. Per cent of patients with abnormally low D_{50C} – that is, hypersensitivity to pentagastrin also shown. In this and subsequent Tables, mean $\pm$ SE values are shown although p values are based on log transformed data (not shown). FH⁺ and FH⁻ = family history of ulcer dyspepsia positive and negative respectively NS = not significant

	Controls	Total DU	Early onset	Late onset	Normosecretors	Hypersecretors	FH ⁺	FH ⁻
n	38	200	120	80	110	90	107	93
D_{50C}	196.4 $\pm$ 31.7 ^a	134.8 $\pm$ 9.9 ^b	135.7 $\pm$ 14.5 ^c	133.5 $\pm$ 11.9 ^d	137.6 $\pm$ 15.6 ^e	131.4 $\pm$ 11.1 ^f	123.3 $\pm$ 12.1 ^g	148.1 $\pm$ 16.1 ^h
Low D_{50C} %	—	27.0	29.2 ^x	23.7 ^x	29.1 ^y	24.4 ^y	29.0 ^z	24.7 ^z

ab, cd p<0.001; ac, ae, ag p<0.005; af p<0.02; ad, ah p<0.04; ef, gh, xx, yy, zz, p=NS, NB cd represents difference in variance, see text.

Table 2 D_{50C} (mean $\pm$ SE ng/kg/h) in duodenal ulcer patients subdivided into early and late onset subjects. FH^+ and FH^- = family history of ulcer dyspepsia positive and negative respectively. NS = not significant. See also Table 1

	Early onset	Late onset	p
Normosecretors	157.6 $\pm$ 25.7 ^a	113.7 $\pm$ 14.5 ^e	<0.001
low D_{50C} %	28.3 ^a	30.0 ^e	NS
n	60	50	
Hypersecretors	113.8 $\pm$ 13.1 ^b	166.6 $\pm$ 19.3 ^f	<0.01
low D_{50C} %	30.0 ^a	13.3 ^e	NS
n	60	30	
FH^+	123.1 $\pm$ 16.4 ^c	123.6 $\pm$ 16.1 ^g	<0.006
low D_{50C} %	32.4 ^y	22.2 ^z	NS
n	71	36	
FH^-	153.9 $\pm$ 26.5 ^d	141.7 $\pm$ 17.2 ^h	<0.07
low D_{50C} %	24.5 ^y	25.0 ^z	NS
n	49	44	

ef p<0.02; ab, cd, gh, ww, xx, yy, zz p=NS

Compared with normal controls: b, c, e, p<0.004; a, d, g p<0.04;

f, h p=NS.

patients with a positive family history of ulcer dyspepsia, the normosecretors had significantly lower D_{50C} than the hypersecretors. Interestingly these late onset, familial ulcer dyspepsia positive normosecretors had the lowest D_{50C} amongst all the various subgroups of duodenal ulcer (Table 3).

PROPORTION OF PATIENTS WITH ABNORMALLY LOW D_{50C}

D_{50C} was considered abnormally low if it was less than 50 ng/kg/h (the lowest value amongst the controls was 55 ng/kg/h). Of the total 200 patients with duodenal ulcer 27% had abnormally low D_{50C} . No difference in the proportion of patients with abnormally low D_{50C} could be found amongst the various subgroups of duodenal ulcer (Tables 1, 2, and 3).

Table 3 D_{50C} (mean $\pm$ SE) in duodenal ulcer (DU) patients further broken down into various subgroups. Per cent of patients with abnormally low D_{50C} also shown. FH^+ and FH^- = family history of ulcer dyspepsia positive and negative respectively. NS = not significant. See also Table 1.

	All duodenal ulcer		Early onset		Late onset	
	FH^+	FH^-	FH^+	FH^-	FH^+	FH^-
Normosecretors	112.1 $\pm$ 18.8 ^a	163.2 $\pm$ 24.5 ^b	127.5 $\pm$ 29.0 ^c	199.7 $\pm$ 46.0 ^d	85.2 $\pm$ 9.3 ^e	132.7 $\pm$ 22.8 ^f
low D_{50C} %	32.7	25.4	34.3	20.0	30.0	30.0
n	55	55	35	25	20	30
Hypersecretors	135.0 $\pm$ 15.0 ^g	126.4 $\pm$ 16.7 ^h	118.8 $\pm$ 16.3 ⁱ	106.3 $\pm$ 22.2 ^j	171.6 $\pm$ 34.7 ^k	160.8 $\pm$ 22.8 ^l
low D_{50C} %	25.0	23.7	30.6	29.2	12.5	14.3
n	52	38	36	24	16	14

ce p<0.001; jl p<0.01; ab, df, gh, ek p<0.05; cd, ef, ij, kl, ag, bh, ik, ci, dj, fl, p=NS

No significant difference in proportion of patients with abnormally low D_{50C} between subgroups. Compared with normal controls:

a, c, e, j p<0.004; f, g, h, i p<0.04; b, d, k, l NS.

Discussion

Using a large series of patients and stringent criteria in accepting individual values of D_{50C} (dose of pentagastrin required to give 50% of maximal acid output after correction for basal output), the present study confirms the original report of Isenberg *et al*¹ that patients with duodenal ulcer as a group have significantly lower D_{50} than normal, indicating the occurrence of abnormal hypersensitivity to pentagastrin among these patients. In the present series, 27% of patients with duodenal ulcer are abnormally sensitive to pentagastrin. Reviewing the literature, although the individual series are small (n=15–25), there appears to be a distinct variation in the proportion of patients with duodenal ulcer who possess this physiological abnormality, and the range is between 0% and 45%.⁶ While the methodologies may be different, another explanation is that the wide variation may be the result of interpopulation and ethnic differences.⁶ One example of such differences was the observation that Scottish patients with duodenal ulcer had significantly larger parietal cell mass²¹ and larger maximal acid output despite correction for body size¹⁸ than Chinese patients with this disease.

Previous studies^{10–12} have shown that patients whose onset of ulcer symptoms begin at ≤ 30 years of age (early onset patients) have an approximately 50% chance of having dyspeptic first degree relatives, as opposed to an approximately 20% chance in those whose onset start at age >30 years (late onset patients). Furthermore, the blood group distribution among early-onset patients is the same as the general population, whereas blood group O predominates in the late onset patients. In the present series of patients, a significant difference in the distribution of D_{50C} occurs between early onset

and late onset patients. Interestingly, among patients with normal maximal acid output (MAO), a higher gastrin sensitivity is present in the late onset subjects, whereas among patients with abnormally large MAO, a higher gastrin sensitivity is present in the early onset patients. Furthermore, a positive family history of ulcer dyspepsia imparts a greater gastrin sensitivity to patients with normal MAO (Table 3). In fact, subjects with normal MAO, late onset disease and positive family history have the highest sensitivity to gastrin among all the various subgroups of duodenal ulcer, and constitutes 10% of the total. A positive family history, however, does not contribute to gastrin hypersensitivity in patients with abnormally large MAO. In fact, subjects with abnormally large MAO, early onset disease and negative family history have the second highest sensitivity to gastrin and constitutes another 12% of the total (Table 3).

Thus patients with normal MAO may exhibit increased gastrin sensitivity, and this is related to a familialness for ulcer dyspepsia suggesting a genetic basis, as well as to the lateness in onset of symptoms suggesting an environmental origin in addition. On the other hand, patients with abnormally large MAO may also have increased gastrin sensitivity, and it appears that this develops early in life, probably under the influence of environmental factors.

In most series of duodenal ulcers, a normal maximal acid output occurs at a frequency of between 50–80%.⁶ If the majority of patients with duodenal ulcer have normal acid secretory capacity, why do duodenal ulcers develop? It is pertinent perhaps to point out that an abnormally large parietal cell mass, as reflected by an abnormally large maximal acid output,^{21 22} is not the only cause of hyperacidity. It has been shown that patients with normal maximal acid output could have (1) increased basal acid output;^{16 23} (2) increased acid response to food teasing¹⁶ and to hypothalamic stress induced by insulin hypoglycaemia,¹⁷ both suggesting that a central nervous stimulus may lead to hyperacidity in such patients; (3) postprandial hypergastrinaemia^{24 25} and abnormal autoregulation of gastrin release,²⁶ both of which may theoretically lead to postprandial hyperacidity; (4) increased peptone stimulated acid secretion;^{26 27} and (5) increased gastric emptying and duodenal acid load.²⁷

This study shows that some patients with normal maximal acid output may have increased sensitivity to gastrin, and contributes yet another explanation for the occurrence of 'hyperacidity' in such individuals.

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