Clinical trial

Effect of proximal gastric vagotomy and anticholinergics on the acid and gastrin responses to sham feeding in duodenal ulcer patients¹

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SUMMARY Plasma gastrin concentrations and gastric acid output after modified sham feeding were determined in 20 duodenal ulcer patients. Sham feeding produced an acid response corresponding to 40–68% of the maximal acid output after pentagastrin stimulation, with no significant increase of plasma gastrin concentrations. In eight patients proximal gastric vagotomy almost abolished the acid responses to both insulin hypoglycaemia and sham feeding. Sham feeding in the vagotomised patients did not change the gastrin concentrations in plasma. After pretreatment with benzilium, an anticholinergic with minimal central nervous effects, plasma gastrin concentrations increased after sham feeding. The study confirms that sham feeding is a poor stimulus for gastrin release in duodenal ulcer patients, and supports a cholinergic inhibition of gastrin release. Intravenous injection of benzilium bromide in a dose close to 70 µg/kg, and atropine in the low dose of 30 µg/kg inhibited the acid response to sham feeding by about 65%. Atropine in a dose of 50 µg/kg virtually abolished the acid sham feeding response, possibly owing to ganglionic or central nervous blockade. Vagal activation of the acid secretory glands does not seem to involve a purely cholinergic neurotransmission.

Vagal activation results in gastric acid secretion by direct nervous stimulation of the parietal cell area and by gastrin released mainly from the antrum, both in dogs (Nilsson *et al.*, 1972; Tepperman *et al.*, 1972) and in duodenal ulcer patients (Stadil and Rehfeld, 1972; Knutson *et al.*, 1974a). In man vagal activation by sham feeding seems to release only very small amounts of established gastrins if any (Stenquist *et al.*, 1979). However, in duodenal ulcer patients after antrectomy the reduction in acid response to sham feeding appears to be greater than the reduction in maximal acid output to pentagastrin (Knutson and Olbe, 1974). This indicates that an antral factor—probably some form of gastrin—contributes to the acid secretion induced by sham

feeding. The substantial acid response to sham feeding in antrectomised patients suggests that the direct nervous stimulation of the parietal cells is the most important factor in the acid response to vagal stimulation in man. This interpretation is in accordance with the very low gastric acid responses to sham feeding preliminarily reported after proximal gastric vagotomy in duodenal ulcer patients (Knutson and Olbe, 1973; Richardson and Feldman, 1978; Stenquist *et al.*, 1978a).

According to classic concepts, the vagal activation of acid secretion is transmitted *via* cholinergic mechanisms. Thus both acid secretion and the gastrin increment after sham feeding in the dog are abolished by atropinisation (Nilsson *et al.*, 1972). In man, however, atropine enhances the gastrin responses to insulin hypoglycaemia (Farooq and Walsh, 1975) and to sham feeding (Feldman *et al.*, 1979).

The present study concerns the effects of proximal gastric vagotomy and anticholinergics on gastric acid secretion and plasma gastrin concentrations evoked by sham feeding in duodenal ulcer patients.

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Methods

PATIENTS

Twenty male patients, mean age 44 years, with recurrent duodenal ulcer disease participated in the study. Eight patients, mean age 40 years (range 25-57 years), were studied before and after proximal gastric vagotomy without a drainage procedure (Grötzinger *et al.*, 1977). Twelve men, mean age 48 years (range 30-69 years), were examined before and after atropinisation and seven men, mean age 51 years (range 30-69 years), were examined before and after administration of benzilium bromide (Parke, Davis & Co.).

The diagnosis was based on the history and on endoscopic and/or barium meal examinations and confirmed at operation in the vagotomised patients. All patients were asymptomatic at the time of the investigation. The experiments involving atropine or benzilium were performed in random order on separate days. In the vagotomised patients the experiments were carried out about six weeks after surgery.

Each patient was informed of the purely scientific purpose of the investigation and agreed to take part. The studies were approved by the Ethical Committee of the Faculty of Medicine, University of Göteborg.

SHAM FEEDING

Details of sham feeding by the 'chew-and-spit' technique have been published previously (Stenquist *et al.*, 1978a,b). This modified sham feeding results in an acid secretion equivalent to that seen in response to adequate sham feeding (Stenquist *et al.*, 1978b). A double-lumen nasogastric tube was passed for acid collection and the basal acid secretion was determined for one-and-a-half hours. The patients were served a hamburger and omelet meal to chew and spit for 15 minutes. They were instructed not to swallow the food and to rinse their mouths frequently with water. During the sham feeding period a small amount of food ($\frac{1}{2}$ -1 ml/15 minutes) reached the stomach in most experiments.

Basal acid output was defined as the output during the last half hour preceding the sham feeding. The acid secretion in response to sham feeding was followed for two hours. The peak acid output in response to sham feeding (PAO_{Sh}) was defined as the sum of the two highest consecutive 15 minute gastric acid outputs after the start of sham feeding.

The effect of cholinergic blockade was tested with either atropine or benzilium, a quaternary antimuscarinic drug with minimal cerebral actions. The anticholinergics were given in two separate intravenous injections. The first injection of 1 mg was given 45 minutes before and the second injection

five minutes before the sham feeding. In the atropine trial the second injection was either 1 mg or 2.5 mg and in the benzilium experiments it was either 1 mg, 2 mg, or 4 mg. When the effect of cholinergic blockade on basal acid secretion was studied, the last 30 minutes of the first and second 45 minute period of basal secretion collection were compared in the same test, as basal levels of acid secretion in the individual patient varied from test to test. Sham feeding was also performed before and after denervation of the acid-producing part of the stomach, proximal gastric vagotomy without a drainage procedure (PGV).

INSULIN TESTS

In patients subjected to PGV, postoperative insulin tests were carried out on a separate day. The basal secretion was collected for at least $1\frac{1}{2}$ hours. The basal acid output was defined as the output during the last half hour preceding the insulin injection. After intravenous injection of insulin (0.2 U/kg) acid secretion was determined for two hours. The peak 30 minute gastric acid output after insulin injection (PAO_{Ins}) was determined. All patients showed clear signs of hypoglycaemia. Multiple criteria were applied for qualitative interpretation of the insulin test, which was considered positive if two or more of seven criteria were satisfied (Stenquist *et al.*, 1978a). The peak post-insulin increase over basal acid output ($\Delta\text{PAO}_{\text{Ins}}$) was calculated.

DETERMINATION OF MAXIMAL GASTRIC ACID RESPONSE TO PENTAGASTRIN

The maximal secretory rate evoked by pentagastrin was determined in all patients. The basal acid secretion was collected for one hour. Gastrin pentapeptide (Peptavlon, ICI) was then infused in a dose of 90 $\mu\text{g/h}$ at a constant rate for 45 minutes, followed by 300 $\mu\text{g/h}$ for an additional 60 minutes (Bergegårdh *et al.*, 1976). The peak acid response to pentagastrin (PAO_{Pg}) was defined as the sum of the two highest consecutive 15 minute acid outputs.

DETERMINATION OF ACID SECRETION

Any anticholinergic medication was stopped at least two days before the tests. After an overnight fast, a nasogastric tube was placed in the antrum under fluoroscopic control. Residual gastric contents were discarded and the gastric juice was collected by a suction pump in 15 minute periods. An aqueous solution of phenol red (8 mg/l) was continuously infused into the stomach at a constant rate of 225 ml/15 minutes. The amount of acid in each 15 minute sample was determined by potentiometric titration to pH 7.0 with 0.1 mol/l sodium hydroxide. The results were corrected for losses of gastric contents

to the duodenum by spectrophotometric determination of the recovery of phenol red.

GASTRIN DETERMINATION

Blood samples were drawn *via* an indwelling forearm vein catheter 10 minutes before gastric intubation. Samples were then taken at the beginning of every 15 minute period throughout the experiment except for the 30 minutes after the start of sham feeding, when samples were drawn at least every five minutes. In the insulin experiments samples were drawn every 10 minutes after the insulin injection. The plasma of each sample was separated by centrifugation in lithium-heparin-coated tubes within 15 minutes and stored at -20°C until assayed.

The gastrin concentrations were measured radioimmunochemically with antiserum 2604 of Rehfeld *et al.* (1972). The assay measures the four main components of gastrin in plasma (Rehfeld *et al.*, 1974) with equimolar potency (Rehfeld, 1976). Further details of the radioimmunoassay procedure have been given elsewhere (Rehfeld and Stadil, 1973.)

The gastrin concentration in the fasting state was defined as the mean of the two gastrin values obtained before gastric intubation. The basal gastrin concentration was defined as the mean of the two gastrin measurements obtained before sham feeding and in the anticholinergic experiments as the mean of the two plasma gastrin concentrations in the last 30 minutes of the first 45 minute period of the basal period in the same test. The mean gastrin concentration for each 15 minute period was calculated and the peak value after sham feeding was noted. Integrated gastrin responses (0-60 minutes) to sham feeding were calculated as described (Richardson *et al.*, 1976).

CALCULATIONS

In each group of sham feeding experiments and in the insulin experiments the significance of difference in acid secretion and plasma gastrin between basal and peak levels and in integrated gastrin responses was tested by Wilcoxon's matched-pairs signed-ranks test or the Mann-Whitney U-test (Siegel, 1956) when appropriate. The latter test was also used to evaluate differences between groups. A P value <0.05 was regarded as significant.

Results

EFFECT OF PROXIMAL GASTRIC VAGOTOMY ON ACID AND GASTRIN RESPONSES TO INSULIN HYPOGLYCAEMIA AND SHAM FEEDING

In eight duodenal ulcer patients PGV reduced the mean maximal response to pentagastrin by 50% (range 31-83%), from a mean of 21.3 to 10.6

mmol/30 min ($P < 0.01$). In four patients all criteria for interpretation of the insulin test were negative and in the other four patients only one criterion was judged positive, suggesting that the vagal denervation of the parietal cell area was complete in all patients. The mean $\Delta \text{PAO}_{\text{Ins}}$ was 0.22 mmol/30 min. An increase in plasma gastrin after insulin injection was found in five out of six patients (Fig. 1). The mean phenol red recovery in the insulin tests was 99%.

Fig. 1 Mean plasma gastrin level in response to intravenous insulin (Ins) 0.2 U/kg b.w. in six duodenal ulcer (DU) patients after proximal gastric vagotomy. In this and the following figures, the vertical bars indicate the standard errors of the means.

Before operation, sham feeding resulted in a significant ($P < 0.01$) increase in acid output. The mean PAO_{Sh} amounted to 14.3 mmol/30 min, corresponding to 67% of the mean peak pentagastrin response (21.3 mmol/30 min). PGV almost completely abolished the basal secretion and peak acid output after sham feeding (mean reduction 94 and 97%, respectively) (Fig. 2). The mean phenol red recovery in the sham feeding experiments was 92% pre-operatively and 98% after PGV.

Before surgery sham feeding did not alter the gastrin concentrations (Fig. 2). After vagotomy fasting gastrin concentrations were significantly raised ($P < 0.02$), although the gastrin concentrations in the basal period immediately before sham feeding were not significantly raised. No significant change in plasma gastrin was found after sham feeding (Fig. 2).

EFFECT OF ANTICHOLINERGICS ON ACID AND PLASMA GASTRIN RESPONSES TO SHAM FEEDING

Atropine (Fig. 3, Table).

In control studies sham feeding in 12 duodenal ulcer patients significantly ($P < 0.01$) increased the gastric acid secretion. The peak acid response was about 45% of the maximal acid response to pentagastrin.

Fig. 2 Mean plasma gastrin level and acid output in response to sham feeding (Sh) before and after proximal gastric vagotomy in eight duodenal ulcer patients with negative insulin tests.

Sham feeding did not significantly change the gastrin concentrations in plasma.

In the experiments with atropine 1.0 mg intravenously inhibited the basal acid secretion by 68% ($P < 0.01$) in 12 duodenal ulcer patients, but the plasma gastrin levels were not significantly changed. The subsequent intravenous injection of 1.0 mg atropine five minutes before sham feeding suppressed the mean PAO_{Sh} by 68% (range 46–99%) ($P < 0.05$)

compared with control experiments in six duodenal ulcer patients. The higher dose of intravenous atropine (2.5 mg) injected five minutes before sham feeding inhibited the mean PAO_{Sh} by 83% ($P < 0.05$) in another six duodenal ulcer patients. In four patients the inhibition amounted to more than 90% and in the remaining two patients the inhibition was 82 and 54%. The mean phenol red recovery was 90%. The integrated gastrin responses to sham feeding in the control studies (mean ($\pm$ SEM) 0.23 ± 0.11 ng $\cdot$ min/ml) were not significantly changed by cholinergic blockade with atropine (mean ($\pm$ SEM) 0.30 ± 0.15 ng $\cdot$ min/ml).

Benzilium (Fig. 4, Table).

In control studies sham feeding in seven duodenal ulcer patients significantly ($P < 0.02$) increased the gastric acid secretion. The acid response to sham feeding was about 60% of the maximal gastric acid response to pentagastrin. The mean phenol red recovery was 91%. Sham feeding did not significantly change the plasma gastrin concentration.

In the experiments with benzilium 1.0 mg intravenously inhibited the basal acid secretion by 60% ($P < 0.02$) in seven duodenal ulcer patients but the plasma gastrin level was unchanged. The subsequent intravenous injection of 1.0 mg benzilium five minutes before sham feeding suppressed the mean PAO_{Sh} by 72% (range 55–95%) ($P < 0.01$) in five duodenal ulcer patients. The higher dose of intravenous benzilium (2.0 mg) injected five minutes before sham feeding inhibited the mean PAO_{Sh} by 63% (range 28–93%) ($P < 0.05$) in six duodenal ulcer patients. In two patients the inhibition amounted to only about 30%. The mean phenol red recovery was 88%. In the two patients in whom the acid sham feeding response was only moderately inhibited (30% inhibition) by pretreatment with 1+2 mg benzilium the experiments were repeated after pretreatment of the patients with

Table Effects of anticholinergics on acid secretory response to sham feeding (Sh) in duodenal ulcer (DU) patients*

Group	Control experiment (without anticholinergic) $PAO_{Sh} \uparrow$ 100 $PAO_{Pg} \uparrow$ (%)	PAO_{Sh} (mmol/30 min)	Sh + anticholi- nergic PAO_{Sh} (mmol/30 min)	Mean inhibition (%)
DU patients (6)	40 $\pm$ 8	10.3 $\pm$ 2.8	3.3 $\pm$ 1.8	68
1.0 mg atropine				
DU patients (6)	55 $\pm$ 9	11.6 $\pm$ 1.7	2.0 $\pm$ 1.2	83
2.5 mg atropine				
DU patients (5)	60 $\pm$ 11	13.0 $\pm$ 2.4	3.6 $\pm$ 1.5	72
1.0 mg benzilium				
DU patients (6)	68 $\pm$ 10	15.8 $\pm$ 1.7	5.8 $\pm$ 2.1	63
2.0 mg benzilium				

*The values for acid output represent means ($\pm$ SEM).

$\uparrow PAO_{Sh}$, peak acid output evoked by sham feeding.

$\uparrow PAO_{Pg}$, peak acid output evoked by pentagastrin.

1+4 mg benzonium. A substantial acid sham feeding response still remained (Fig. 5). The integrated gastrin responses to sham feeding were significantly higher after pretreatment with benzonium (mean ($\pm$ SEM) 1.27 ± 0.39 ng $\cdot$ min/ml, $P < 0.02$) than in control experiments (mean ($\pm$ SEM) 0.33 ± 0.13 ng $\cdot$ min/ml).

Discussion

In dogs it has been clearly established that vagal activation of gastric acid secretion is mediated by the combined actions of a direct nervous excitation of the parietal cell area and vagally released gastrin (Olbe and Knutson, 1976). Sham feeding experiments have indicated, however, that vagal release of gastrin in man is of minor importance for the stimulation of gastric acid secretion by vagal activation. Thus, the gastric acid response to sham feeding in duodenal ulcer patients was suppressed by antral acidification (Knutson *et al.*, 1974b) and was more suppressed than the maximal acid response to pentagastrin by antrectomy (Knutson and Olbe, 1974). The suppressions were, however, slight. Sham feeding

has previously resulted in a gastrin response in duodenal ulcer patients (Knutson *et al.*, 1974a; Mayer *et al.*, 1974) and varying gastrin increments in serum in healthy subjects (Mayer *et al.*, 1974; Richardson *et al.*, 1977; Feldman *et al.*, 1979). In a recent study sham feeding in duodenal ulcer patients did not significantly increase plasma gastrins (Stenquist *et al.*, 1979), indicating either that very small gastrin increments (in range of a few pg/ml) have a slight acid stimulatory effect or that hitherto unknown gastrin components are released.

The present study confirms that the gastrin response is poor or non-existent after sham feeding in duodenal ulcer patients. After proximal gastric vagotomy no significant increase of the gastrin concentrations in plasma was detectable in the basal period and sham feeding did not induce significant plasma gastrin increments. Thus, the vagus does not seem to mediate fundic inhibition of gastrin release (Yamagishi *et al.*, 1978). A gastrin response to insulin hypoglycaemia after proximal gastric vagotomy—probably mediated *via* adrenaline (Kronborg *et al.*, 1974)—was confirmed by the present study.

In dogs the gastrin response to sham feeding or

Fig. 3 Mean plasma gastrin level and acid output in response to sham feeding (Sh) with (●—●) and without (○—○) intravenous atropine in duodenal ulcer patients. Left panel: 1 + 1 mg atropine (six duodenal ulcer patients). Right panel: 1 + 2.5 mg atropine (six duodenal ulcer patients).

insulin hypoglycaemia seems to originate from the antrum, as antral denervation abolished the responses (Tepperman *et al.*, 1972). Large doses of atropine (70–200 $\mu\text{g/kg}$) inhibited the release of gastrin after sham feeding (Nilsson *et al.*, 1972), insulin hypoglycaemia (Csendes *et al.*, 1972), or a meal (Csendes *et al.*, 1972). However, a small dose of atropine (less than 25 $\mu\text{g/kg}$) enhanced the gastrin response to food in dogs (Impicciatore *et al.*, 1977), as a small dose of atropine in healthy humans enhanced the gastrin responses to sham feeding (Feldman *et al.*, 1979), insulin hypoglycaemia (Farooq and Walsh, 1975), and a meal (Walsh *et al.* 1971). In view of the recent demonstration of cholinergic inhibition of gastrin release (Taylor *et al.*, 1977), it seems likely that vagal stimulation induces a non-cholinergic gastrin release.

The atropine doses used in the present study, corresponding to about 30 and 50 $\mu\text{g/kg}$, resulted in no gastrin response to sham feeding, while the

integrated gastrin responses to sham feeding significantly increased in duodenal ulcer patients pretreated with benzilonium. The absence of gastrin response to sham feeding after atropine pretreatment may be due to ganglionic or central nervous blockade of vagal release of gastrin. The facilitated release after benzilonium pretreatment strengthens the view that cholinergic inhibition may interfere with the vagal release of gastrin.

In dogs vagally released gastrin did not stimulate acid secretion after fundic denervation (Tepperman *et al.*, 1972). The failure seems to be due to reduced sensitivity of the vagotomised fundic area to gastrin (Ernäs and Grossman, 1967) and to vagal release of an inhibitory substance, vagogastrone (Preshaw, 1973; Sjödin, 1975). A weak vagogastrone mechanism exists also in duodenal ulcer patients (Stenquist *et al.*, 1978a). It may decrease the acid response to vagal stimulation after complete proximal gastric vagotomy by blocking the action of

Fig. 4 Mean plasma gastrin level and acid output in response to sham feeding (Sh) with (●—●) and without (○—○) intravenous benzilonium in duodenal ulcer patients. Left panel: 1 + 1 mg benzilonium (five duodenal ulcer patients). Right panel: 1 + 2 mg benzilonium (six duodenal ulcer patients).

any released gastrins. In the present study the acid responses to both insulin hypoglycaemia and sham feeding were almost abolished after proximal gastric vagotomy, although differences between the two responses may appear after the vagotomy (Stenquist *et al.*, 1978a).

Fig. 5 Effect of intravenous injection of anticholinergics on peak acid response to sham feeding in two patients.

In dogs, administration of atropine in a large dose (70–100 $\mu\text{g/kg}$) completely abolishes the acid secretion induced by sham feeding (Nilsson *et al.*, 1972), or insulin hypoglycaemia (Csendes *et al.*, 1972). In man a low dose of atropine (15 $\mu\text{g/kg}$) inhibited the peak acid response to insulin by 61% (Farooq and Walsh, 1975). In the present study intravenous administration of an anticholinergic with minimal central nervous effects (benzilonium bromide) in doses up to about 70 $\mu\text{g/kg}$ and atropine in low doses inhibited the acid response to sham feeding by about 65% (Table, Fig. 5). All three doses of benzilonium produced the same inhibition of the acid response to sham feeding and, furthermore, small doses of both benzilonium and atropine completely blocked the vagal release of pancreatic polypeptide in response to sham feeding (Schwartz *et al.*, 1979), these findings strongly supporting the fact that the doses of anticholinergics used in the present study produced maximal antimuscarinic effect. These results suggest that the vagal neurotransmission at the acid-secreting glands is only partially cholinergic. It is true that atropine in a large dose almost abolished the acid response to sham feeding. Such a large dose of atropine may, however, induce a cholinergic blockade in the central nervous system. The marked inhibitory effect

of a large dose of atropine on the acid response to sham feeding may be independent of the peripheral vagal neurotransmission.

The direct vagal activation of the acid-secreting glands is apparently not purely cholinergic. The mechanism by which intravenous infusion of the H_2 -receptor antagonist cimetidine in a dose of 100 mg/h markedly inhibited the acid response to sham feeding by 90–100% in duodenal ulcer patients (Schöön and Olbe, 1978) is far from clear, but the results may be interpreted as indicating that the effect of the missing vagal neurotransmitter is sensitive to H_2 -receptor blockade. The recent findings of heptadecapeptide gastrin in the vagal nerve of animals and man (Uvnäs-Wallensten *et al.*, 1977) may then support speculations that gastrin participates in the vagal activation of gastric acid secretion both as a hormone released from the antrum and as a vagal neurotransmitter.

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