THE EFFECT OF VAGOTOMY ON THE LOWER PART OF THE ACID DOSE-RESPONSE CURVE TO PENTAGASTRIN IN MAN


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(Received 5 February 1972)

SUMMARY

1. The acid secretory responses to insulin of forty-seven duodenal ulcer patients after truncal vagotomy and drainage were classified according to the criteria of Hollander (1946) into positive or negative.

2. The acid response to ranges of small doses of pentagastrin was studied in these two groups. In the group with a positive acid response after insulin the dose-response pattern to pentagastrin was very similar to that in preoperative patients.

3. In those who failed to satisfy criteria for a positive response after insulin the dose-response curve to pentagastrin appeared to shift to the right. It had a lower level and a smaller slope. Truncal vagotomy appeared to cause an eightfold increase in the threshold dose found in preoperative patients.

4. Supersensitivity of the stomach to small doses of pentagastrin after vagotomy was not apparent in the present study.

Key words: gastric acid secretion, insulin, duodenal ulcers, pentagastrin, truncal vagotomy.

The effects of truncal vagotomy on the gastric acid secretory response to both sub-maximal and maximal doses of pentagastrin in man have been documented (Multicentre Study, 1967; Duthie, Jepson & Johnston, 1967; Jepson & Johnston, 1968), but the effect on the threshold or 'switch-on' dose of pentagastrin required to initiate secretion after vagotomy has not been adequately studied. It is generally agreed that the parietal cells are less sensitive to gastrin and its derivatives after complete vagotomy. Whether this decreased response of the acid-secreting cells is uniform throughout the dose-response curve for pentagastrin is not known. Heathcote, Daly & Gillespie (1965) have, however, suggested that the acid responses to small doses of a gastric acid secretory stimulant are more dependent on cholinergic influence than those obtained with near maximal doses.

In the present paper we describe the lower part of the dose-response curve to pentagastrin.

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after vagotomy in duodenal ulcer patients, and compare the threshold dose in preoperative subjects with that required after complete vagotomy.

MATERIALS AND METHODS

Forty-seven patients were studied after truncal vagotomy and drainage (pyloroplasty in twenty-six, gastro-enterostomy in twenty-one) for duodenal ulcer. Twenty-nine patients were insulin negative by both Hollander's (1946) criteria and by the acid-output criterion proposed by Gillespie, Elder, Smith, Kennedy, Gillespie, Kay & Campbell (1972). The remaining eighteen patients were insulin-positive and fourteen of these also satisfied the acid-output criterion for a positive response.

In each case an insulin test was performed as described by Gillespie, Elder, Gillespie, Kay & Campbell (1970) within the first 10 days of operation, and a pentagastrin infusion with small doses was done within the first month after surgery. The result of the insulin test was always known before the pentagastrin infusion test was performed. If the vagotomy appeared complete (Hollander, 1946) then pentagastrin infusion over the dose range 0.064, 0.128, 0.256 and 0.512 μg h⁻¹ kg⁻¹ was performed. In those who had a positive Hollander response to insulin after vagotomy the small range of doses as described for patients with intact vagal innervation was used, i.e. 0.008–0.064 μg h⁻¹ kg⁻¹. Pilot studies indicated that there was no response over this latter dose range in insulin-negative cases. Doses were given in ascending sequence by doubling the rate of infusion; in twenty-eight patients the initial rate was 10.8 ml/h and in eighteen patients it was 21.6 ml/h. Of the patients who were insulin negative after surgery fifteen commenced at pentagastrin doses of 0.064 μg h⁻¹ kg⁻¹ and fourteen at 0.128 μg h⁻¹ kg⁻¹. All those receiving 0.256 and 0.512 μg h⁻¹ kg⁻¹ had already received one of the lower doses. In the insulin-positive group ten patients began at 0.008, two at 0.016, four at 0.032 and two at 0.064 μg h⁻¹ kg⁻¹. The significance of the acid-output response to low-dose pentagastrin infusion was assessed by the acid output criterion (Gillespie et al., 1972).

Of the twenty-nine insulin-negative cases twenty-three had a preoperative pentagastrin test of maximal acid secretion (6 μg/kg pentagastrin intramuscularly).

RESULTS

Figs. 1 and 2 show the mean ± SD per 10-min period for acid output in each group of post-operative patients. Table 1 shows the results of the application of the acid-output criterion of positive response (Gillespie et al., 1972) to the individual acid-responses to small doses of pentagastrin in patients with negative responses to insulin. When pentagastrin (0.064 μg h⁻¹ kg⁻¹) was infused for 40 min in fifteen patients, three satisfied the criterion for stimulation (Table 1, patients 2, 8 and 9); when 0.128 μg h⁻¹ kg⁻¹ was infused nine of twenty-nine patients, at 0.256 μg h⁻¹ kg⁻¹ twelve of twenty-five, and at 0.512 μg h⁻¹ kg⁻¹ eleven of fourteen satisfied the criterion for stimulation of a significant acid response (P < 0.01).

Similarly, Table 2 shows the results of application of the acid-output criterion to the insulin-positive group who received pentagastrin on the same dosage schedule as preoperative subjects with fully innervated stomachs. When pentagastrin (0.008 μg h⁻¹ kg⁻¹) was infused for 40 min in ten patients, one (Table 2, patient 18) satisfied the criterion for stimulation; at 0.016 μg h⁻¹ kg⁻¹ three of twelve, at 0.032, six of twelve, and at 0.064 eight of thirteen patients satisfied the criterion for stimulation of an acid response significant at less than the 1% level.
FIG. 1. Lower part of acid dose-response curve to pentagastrin in duodenal ulcer patients who were Hollander insulin-negative after truncal vagotomy. Means ± SD are shown. Significant increase in acid output over the basal value occurred when pentagastrin (0.512 μg h⁻¹ kg⁻¹) was infused (P<0.01).

FIG. 2. Lower part of acid dose-response curve to pentagastrin in duodenal ulcer patients who were Hollander insulin-positive after truncal vagotomy. Means ± SD are shown. Significant increase in acid output over basal occurred when pentagastrin (0.064 μg h⁻¹ kg⁻¹) was given (P<0.01).
Threshold and sub-threshold dose of pentagastrin in post-vagotomy subjects

Of those whose vagotomy appeared complete (Table 1) 78% showed a significant increase (\( P<0.01 \)) in acid output when pentagastrin (0-512 \( \mu \text{g h}^{-1} \text{kg}^{-1} \)) was infused, and this dose is therefore suggested as threshold for vagotomized ulcer patients. A significant response was obtained in three of fifteen (20%) when 0.064 \( \mu \text{g h}^{-1} \text{kg}^{-1} \) was infused. It is unlikely, therefore, that this dose would be sub-threshold for all vagotomized or apparently completely vagotomized subjects.

In those whose vagotomy was incomplete a dose–response pattern very similar to that observed in preoperative subjects was noted on insulin testing (Elder, Gillespie, Campbell,
Pentagastrin threshold after vagotomy

**Table 2. Assessment of acid output responses to graded doses of pentagastrin in eighteen patients insulin positive after truncal vagotomy**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean basal output (mEq/10 min)</th>
<th>Mean Pentagastrin dose (μg h⁻¹ kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>8*</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>12</td>
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<tr>
<td>13</td>
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</tr>
<tr>
<td>16</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
<td>+</td>
</tr>
</tbody>
</table>

+: An increase in acid output above the basal value significant at less than the 1% level \((P<0.01)\).

* Female.

Gillespie, Crean & Kay, 1972). Of the insulin-positive subjects tested eight of thirteen (61%) satisfied the criterion for stimulation of acid output when 0.064 μg of pentagastrin h⁻¹ kg⁻¹ was given.

**Effect of truncal vagotomy on the lower part of the dose–response curve to pentagastrin**

The relationship of the acid response to small doses of pentagastrin to the peak acid response was described in subjects with intact vagus nerves (Elder et al., 1972). In the present study a separate group of patients of closely similar age, weight and preoperative maximal acid output to pentagastrin (Table 3) was studied after vagotomy. Interestingly, comparison of the dose response of acid secretion in the two groups (Fig. 3) shows that the dose–response curve to pentagastrin appears to shift to the right after vagotomy, and it was at a considerably lower level, with a smaller slope. Also an eightfold increase in pentagastrin dosage, i.e. from 0.064 to 0.512 μg h⁻¹ kg⁻¹, was required after vagotomy to achieve an acid response significantly greater than the basal secretion with confidence limits at the 1% level.

**DISCUSSION**

There have been no detailed studies published on the lower part of the dose–response curve for acid secretion to pentagastrin after truncal vagotomy in duodenal ulcer patients. In view
of the decrease in maximal acid output to both histamine (Gillespie, Clark, Kay & Tankel, 1960; Gelb, Baronofsky & Janowitz, 1961) and to pentagastrin (Multicentre Study, 1967), it is not surprising that a change has been observed in the dose of pentagastrin required to 'switch-on' acid secretion after vagotomy.

![Graph showing dose-response curves to pentagastrin](image)

**Fig. 3.** Comparison of dose–response curves to pentagastrin in two similar groups of subjects, one before (upper line) and one after (lower line) truncal vagotomy and drainage. Means ± SEM of acid output expressed as percentage of preoperative peak acid output to 6 μg of pentagastrin/kg are shown for each group.

**Table 3.** Comparison of means (±SEM) of age, weight and preoperative peak acid output after pentagastrin (6 μg/kg) in pre- and post-operative groups

<table>
<thead>
<tr>
<th></th>
<th>Preoperative group (n = 29)</th>
<th>Post-operative group (n = 23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.8 ± 2.45</td>
<td>43.4 ± 2.37</td>
<td>N.S.</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.9 ± 2.89</td>
<td>62.75 ± 3.0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Peak acid output (mEq/h)</td>
<td>36.8 ± 3.0</td>
<td>34.7 ± 2.1</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Peak acid output (mEq/h) = 2 × 30-min acid output. N.S. = not significant.

A measure of the pentagastrin dose threshold for stimulation of acid secretion after truncal vagotomy and a comparison of this dose with the preoperative threshold might allow a further estimate of the part played by vagal influence in the sensitivity of parietal cells to gastrin.

Truncal vagotomy appears to cause an approximately eightfold increase in threshold dose of pentagastrin when compared with studies in preoperative patients, i.e. from 0.064 to 0.512 μg h⁻¹ kg⁻¹. Using supra-threshold dose-levels, Konturek, Wysocki & Olesky (1968) also
found a shift to the right in pentagastrin dose-response to vagotomy. In the present study at threshold dose-levels (0.512 μg h⁻¹ kg⁻¹) the vagotomized group were still only producing about 25% of their preoperative peak acid output (Fig. 3). A similar acid output was found when 0.008 μg h⁻¹ kg⁻¹ was infused in preoperative subjects (Fig. 3) corresponding to about 25% of their peak acid output. This suggests that 64 times the dose of pentagastrin after complete vagotomy is required to achieve comparable stimulation at the lower end of the dose–response curve. It must be emphasized, however, that these values are based on relatively small numbers of patients. Measurement of decrease of maximal acid output after operation has not found wide acceptance as an index of complete vagotomy and the wider separation of innervated and denervated groups at the lower end of the dose–response curve to pentagastrin may be more useful. The present studies confirm the suggestion of Heathcote et al. (1965) and of Makhlouf (1968) that the effect of vagotomy on gastric secretory responses to humoral agents is more marked at the lower than at the upper part of the dose–response curve.

The responses in vagotomized subjects varied, some (Table 1) showing stimulation by pentagastrin doses which were threshold for the majority of preoperative subjects. Recent studies have suggested that up to 50% of patients initially insulin negative in the immediate 10 day post-operative period will change to a positive response up to 4 years after vagotomy (Gillespie et al., 1970). It remains to be determined what happens to the pentagastrin threshold dose in such patients, and whether an assessment shortly after operation of the threshold dose for stimulation by pentagastrin will accurately reflect the eventual outcome with respect to the innervation of the stomach, and more importantly, to the development of further ulceration.

Super-sensitivity to pentagastrin after either complete or incomplete vagotomy was not apparent in the present study.

ACKNOWLEDGMENTS

We thank Imperial Chemical Industries for the provision of pentagastrin for this study. Technical assistance in the performance of these tests was willingly provided by Miss A. Halliday of the Department of Surgery, Western Infirmary, and by Mr J. Hearns of the Gastrointestinal Centre, Southern General Hospital, Glasgow. Our thanks are also due to the Department of Medical Illustration, Western Infirmary, for the illustrations.

REFERENCES


