The stomach gastric fistula is anaesthetized with urethane in this study. In this the pH and through prewarmed 34°C. The perfusate 2.0 mg/hr. Infusion minutes before orally administered. SC 15396 (5.5 mg/kg) was used. Although some inhibition appeared to occur, this was not statistically significant. When the dose was raised to 200 mg (11 mg/kg), however, prompt and highly significant inhibition of secretion (Fig. 16) resulted ($p < 0.001$ for 30-minute periods up to two hours after SC 15396). No toxic effects were noted even with this large intravenous dose.

**SUMMARY**

SC 15396 has been shown to exert an inhibitory effect on canine gastric secretion stimulated by gastrin, insulin, and histamine.

During the course of this work, Mr I. B. Macleod was in receipt of a Medical Research Council grant whose financial assistance is gratefully acknowledged.

The authors wish to express their gratitude to Mr M. G. B. Walker for his skilled technical assistance.

**Part III The action in the rat**

**C. G. THOMSON AND W. SIRCUS**

**MATERIALS AND METHODS**

A modification of the anaesthetized rat preparation described by Lai (1964) was used as the assay animal in this study. In this the animal (male, Wistar strain) is anaesthetized with urethane (1.25 g/kg intramuscularly) and is maintained at 34°C throughout the assay. After the oesophagus has been intubated, the stomach is exposed by a midline incision and the duodenum is cannulated. The stomach is washed free of debris with 0.9% NaCl and is then perfused at 1 ml/min with buffered saline, prewarmed to 34°C. The perfusate from the stomach is passed through a microflow pH electrode (EIL GMF 23) and the pH readings are recorded on a chart recorder linked to the meter. The perfusing buffer is phosphate-citrate-saline ($1.54 \times 10^{-3} M \text{Na}_2\text{HPO}_4$; $2.3 \times 10^{-4} M$ citric acid; $1.54 \times 10^{-1} M \text{NaCl}$, $I = 0.160$, pH 6.6) which permits an approximately linear pH response to unit additions of acid over the pH range 6.5 to 3.5, so circumventing the problem of the logarithmic aspect of pH recordings inherent in techniques using pH monitoring of isotonic saline perfusions (see Ghosh and Schild, 1958; Amure and Ginsburg, 1964).

Solutions to be assayed are infused into the external jugular vein, which is maintained patent throughout the day's experiment with a constant slow infusion of 0.9% NaCl. Figure 17 shows a tracing typical of the response obtained to the infusion of gastrin II (Gregory and Tracy, 1964); pH begins to fall from the baseline during the infusion of the test material, and does not return to the original value until some time after the test infusion has been replaced with saline. Since the change in pH is related linearly to the concentration of acid secreted, it is valid to accept the area under the curve (shown in
preparation (Colquhoun, 1963). SC 15396 was dissolved in dimethyl sulphoxide: 0-9% saline (1:1, v/v) and infused into the test animals.

RESULTS

It was found that neither dimethyl sulphoxide-saline alone nor SC 15396 in that medium produced any effect on the basal gastric secretory behaviour of the test animal to which they were administered (Fig. 18). An infusion of gastrin II in dimethyl sulphoxide-saline produced a response identical to that obtained from the same dose of gastrin II in saline in the same animal. It was therefore concluded that dimethyl sulphoxide itself did not influence the gastric secretory response of the test animal.

The results in Table II summarize the findings when SC 15396 was given before the test dose of gastrin II. The 100% response for the animal being tested is taken as that resulting from a dose of gastrin II given before the start of the experiment and shown in the table as the reference dose.

Table III shows the effect of administering SC 15396 to animals in which secretion has already been induced by infusion of gastrin II. Again the response is calculated as a percentage of that produced by a reference dose of gastrin II given to the animal before the test dose.

It is evident that SC 15396 is able to decrease or to abolish completely the normal secretory response to gastrin II when the drug is given before and also when it follows immediately the test dose of gastrin II. We have also found in one experiment, when the drug and the hormone were infused simultaneously, that the drug is inhibitory in this situation. (A drug/  

---

**FIG. 17. Typical pH recording obtained in response to infusion of 0·3 μg gastrin II. The vertical divisions each represent 30 minute intervals. The horizontal divisions each represent 0·2 pH.**

---

### TABLE II

**EFFECT OF SC 15396 ON THE PREVENTION OF GASTRIN-INDUCED SECRETION.**

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>Reference Dose Gastrin II (μg)</th>
<th>Time (min)</th>
<th>SC 15396 (mg)</th>
<th>Gastrin II (μg)</th>
<th>Drug-Hormone Molar Ratio/Kg</th>
<th>Response (% Reference Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0·3</td>
<td>0</td>
<td>0·75</td>
<td>0·3</td>
<td>11·70 × 10^4</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>0·3</td>
<td>60</td>
<td>0·9</td>
<td>0·3</td>
<td>11·65 × 10^4</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>0·3</td>
<td>55</td>
<td>1·0</td>
<td>0·3</td>
<td>27·90 × 10^4</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0·3</td>
<td>55</td>
<td>1·25</td>
<td>0·3</td>
<td>11·56 × 10^4</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>0·3</td>
<td>60</td>
<td>2·0</td>
<td>0·3</td>
<td>38·67 × 10^4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0·3</td>
<td>45</td>
<td>0·9</td>
<td>0·3</td>
<td>6·14 × 10^4</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>0·6</td>
<td>0</td>
<td>0·9</td>
<td>0·3</td>
<td>5·29 × 10^4</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>0·3</td>
<td>55</td>
<td>0·9</td>
<td>0·6</td>
<td>3·07 × 10^4</td>
<td>30</td>
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<tr>
<td>7</td>
<td>0·6</td>
<td>110</td>
<td>0·9</td>
<td>1·2</td>
<td>2·96 × 10^4</td>
<td>75</td>
</tr>
</tbody>
</table>

*1The drug-hormone molar ratio/kg is calculated from the dose of drug given and the amount of hormone infused after the injection of the drug at the time intervals shown.*
Effects of SC 15396 on gastric secretion

Effects of SC 15396 on gastric secretion

FIG. 18. Recording obtained in response to infusion of 1·2 ml dimethyl sulphoxide, 0·9% NaCl (1:1, v/v) and to
3·0 mg SC 15396 in that medium. Chart calibrations as in Figure 17.

Rat No. 6 3 4 8 9

Blocking secretion that has already commenced (for example, see the results on rats 3 and 6 in both Tables). It is, however, clear that there is between-animal variation in sensitivity to the drug, as comparison of rats 2 and 4 (Table II) demonstrates.

In practice, it appears that a drug-hormone molar ratio/kg in excess of $50 \times 10^4$ is capable of blocking entirely secretion that has already commenced, providing that the drug is given directly after the test dose of hormone, while at lower drug-hormone ratios only partial suppression is achieved (rat 8, Table III).

The ratio required to prevent completely the normal secretory response to gastrin when the drug

TABLE III

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>Reference Dose</th>
<th>Time</th>
<th>Gastrin II</th>
<th>SC 15396</th>
<th>Drug-Hormone Molar Ratio/kg</th>
<th>Response (%) Reference Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3</td>
<td>0</td>
<td>0.3</td>
<td>0.75</td>
<td>11.70 \times 10^4</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>15</td>
<td>0.3</td>
<td>0.9</td>
<td>11.65 \times 10^4</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>0</td>
<td>0.3</td>
<td>1.0</td>
<td>27.90 \times 10^4</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>15</td>
<td>0.3</td>
<td>1.25</td>
<td>11.56 \times 10^4</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
<td>0</td>
<td>0.3</td>
<td>2.0</td>
<td>38.67 \times 10^4</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>0.3</td>
<td>15</td>
<td>0.3</td>
<td>3.0</td>
<td>56.60 \times 10^4</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0.3</td>
<td>0</td>
<td>0.3</td>
<td>3.5</td>
<td>65.17 \times 10^4</td>
<td>0</td>
</tr>
</tbody>
</table>

The drug-hormone molar ratio/kg is calculated from the dose of SC 15396 given and from the amount of gastrin II infused immediately before the drug. The rat numbers identify the animals referred to in Table II.

The inhibitory action on gastrin-provoked secretion persists for at least two hours after giving the drug (rats nos. 6 and 7, Table II).

DISCUSSION

It appears that a significant factor influencing the extent of inhibition produced by SC 15396 is the ratio of the drug to the test dose of gastrin II, the inhibition increasing as the ratio increases. The drug is more effective in preventing secretion than in hormone molar ratio/kg of $64.1 \times 10^4$ resulted in complete suppression of the normal secretory response.) The inhibitory action on gastrin-provoked secretion persists for at least two hours after giving the drug (rats nos. 6 and 7, Table II).

CONCLUSION

This study of the action of SC 15396 on gastrin-stimulated gastric secretion of the anaesthetized rat agrees with the results reported in conscious dogs (Bedi et al, 1967) that the drug is capable of preventing or abolishing such secretion.

We are indebted to Professor R. A. Gregory of Liverpool for the sample of gastrin II used as the reference standard throughout this study.
Discussion

In the test situations described in this communication, SC 15396 effectively depressed the secretory response to gastrin II in both the dog and the rat, and to ICI 50123 (pentagastrin, Peptavlon) in the dog. When given intravenously to dogs in a dosage of 2-2 to 4-2 mg/kg, it promptly inhibited secretion already established by prior infusion or injection of gastrin II, confirming the results reported by Bedi et al (1967) who used doses of 0-75 to 1-5 mg/kg body weight. Intravenous injection of 1 mg/kg SC 15396 in dogs also promptly depressed the response to a constant infusion of Peptavlon. SC 15396 also delayed and depressed the promotion of secretion when administered before the stimulant. The results of Thomson and Sircus indicate that in the rat SC 15396 depressed the induction of secretion by gastrin more effectively than it inhibited already established secretion.

The inhibitory action of SC 15396 on gastrin- or Peptavlon-stimulated secretion was clearly demonstrable when it was given orally or intragastrically. The experiments of Macleod and Hill on pouch dogs indicate marked inhibitory activity against gastrin-stimulated secretion over the dose range 5 to 12 mg/kg body weight, while Connell’s results in fistula dogs show increasing inhibitory action against maximal Peptavlon-stimulated secretion over the dose range 5 to 20 mg/kg body weight. Oral doses lower than 5 mg/kg were not used by Macleod and Hill, but Connell reports 33% inhibition of submaximal Peptavlon-stimulated secretion by oral doses of 1 mg/kg body weight. In the experiments reported by Macleod and Hill a short delay occurred before the inhibition appeared. As inhibitory action was demonstrated upon the secretory response of a fundic pouch, the drug must be absorbed from the gastrointestinal tract, and the delay may therefore represent absorption time. The site of such absorption is, however, not established.

Insulin-stimulated secretion was markedly inhibited by intravenous injection of SC 15396 in a dosage of 3-1 to 4-2 mg/kg, and by oral administration in a dosage of 20 mg/kg. The theoretical possibility exists in the intravenous experiments that SC 15396 directly inactivated the insulin, thus producing an apparent rather than a true inhibition. This possibility is discounted by the fact that similar blood sugar levels were achieved in experiments whether or not SC 15396 was given, and by the fact that altering the timing of the injection of SC 15396 to 15 minutes before or 10 minutes after the insulin injection did not influence the results.

The demonstration that SC 15396 inhibits insulin-stimulated secretion in these doses does not in itself disprove the claim put forward by Bedi and his colleagues (1967) that it is a specific antagonist for gastrin. It is probable that a major portion of insulin-stimulated secretion results from vagal release of gastrin (Maung Pe Thein and Schofield, 1959). However, vagal nerve stimulation also has a direct action on parietal cells (Olbe, 1964), and in the experiments of Macleod and Hill, insulin still induced a small secretion in dogs with complete antrectomy. SC 15396 markedly inhibited this secretion, suggesting that its action extends to the direct phase of vagal-stimulated secretion, though the presence of gastrin-secreting mucosa in the duodenum of these dogs was not excluded.

The evidence presented in the communications of Connell and of Macleod and Hill indicates that histamine-stimulated secretion can be inhibited by SC 15396 but that larger doses of the drug are required than when gastrin is the stimulant. Using large oral doses (5 to 12 mg/kg) an inhibitory effect is clearly demonstrable on pouch dogs, and denervated pouches appear to be more sensitive to inhibition than do innervated pouches. Prior oral or intragastric administration of SC 15396 could not be demonstrated to inhibit secretion in the gastric fistula dog. However, when the drug was administered intravenously to fistula dogs during established histamine-stimulated secretion, inhibition could be demonstrated. The inhibition shown in the experiments of Connell using 1 mg/kg body weight SC 15396 against histamine infusion of 1-0 mg/hr could have occurred by chance. Macleod and Hill, however, using a histamine infusion rate of 2-0 mg/hr as their secretory stimulus, demonstrated statistically significant inhibition of secretion with an intravenous dose of 11 mg/kg body weight of SC 15396.

The described variability of the inhibitory influence of SC 15396 upon the action of histamine may be explained by a failure to achieve an adequate molar ratio of drug to secretagogue. The rat studies suggest that this ratio/kg body weight must be around 20 × 10^4 to guarantee adequate inhibition of gastrin-stimulated secretion. When Macleod and Hill’s studies with gastrin II are analysed similarly the drug-hormone molar ratio for dogs is found to be of the same order (17 × 10^4 to 30 × 10^4). A similar calculation for Peptavlon can only be made on Connell’s experiments, but these suggest that the effective drug-secretagogue ratio in this case is
about $2 \times 10^4$. When the ratio is calculated for histamine in the experiments of Connell, and of Macleod and Hill, a drug-secretagogue molar ratio of approximately $0.005 \times 10^4$ is found in those experiments where inhibition was not achieved, whereas in the experiments where adequate (50%) inhibition was obtained, a molar ratio of $0.02 \times 10^4$ is found.

It is therefore possible that there is a critical molar ratio of drug to secretogogue for effective inhibitory action of SC 15396, which is independent of the animal species and is characteristic of the secretogogue.

The finding of Bedi and his colleagues (1967) that SC 15396 had no action on histamine-stimulated secretion in dogs is probably explained by the fact that they used smaller doses of SC 15396 than those reported here, and thus failed to achieve a drug-secretagogue molar ratio sufficient to demonstrate inhibition.

The finding of Macleod and Hill that denervated fundic pouches undergoing histamine stimulation are more sensitive than innervated pouches to inhibition by SC 15396 is of interest, though its significance is not yet clear. It probably reflects an increased susceptibility of the denervated parietal cells, relatively poorly primed because of the lack of vagal ‘tonic’ impulses. Macleod and Hill could not demonstrate a similar protective effect of innervation when the secretory stimulus was gastrin II. However, Davison et al. (1967) and Bedi et al. (1967), using much smaller doses of SC 15396, demonstrated the same effect in pouch dogs when the secretory stimulus was feeding, the major secretory stimulus under such conditions being endogenous gastrin. In Macleod and Hill’s experiments, much higher drug-hormone molar ratios were achieved in the experiments using gastrin II than in those using histamine, and it is possible that the protective effect of innervation becomes swamped at these higher ratios.

The difficulty in demonstrating inhibition of histamine-stimulated secretion in gastric fistula dogs by oral intragastric administration of SC 15396 deserves further comment. The experimental situation differed from that pertaining in the pouch dogs in that the SC 15396 was administered one hour before beginning stimulation, and thus a direct comparison with the pouch dog experiments cannot be made. Macleod and Hill noted drug particles returning in the secretion of their fistula dogs, and attribute part of their failure to demonstrate inhibition in this situation to incomplete absorption and failure to achieve an effective drug-hormone molar ratio. Connell, however, did not have this technical difficulty and also failed to demonstrate inhibition.

We can offer no satisfactory explanation for this inability to demonstrate inhibition in the fistula dogs when the drug is administered orally before histamine stimulation. An explanation may be forthcoming when quantitative techniques to determine blood levels of SC 15396 become available.

The mode of action of SC 15396 is uncertain. The evidence presented in this communication suggests that it acts at the parietal cell level, though the possibility that it may also prevent release of gastrin from the antrum is not excluded. In the experiments of Macleod and Hill very prolonged inhibition was noted when large doses of SC 15396 were used, suggesting a possible toxic action on the parietal cell in these doses. Clarification of this possibility is difficult in dogs because of the long time periods involved, but is obviously necessary. The fact that secretion was restored in three out of four experiments by intravenous injection of carbachol suggests that a purely toxic action of SC 15396 is unlikely. Further support for this view may be gained by referring to the results from rat 7 (Thomson and Sircus, Table I) which demonstrate that, provided the dose of secretagogue is sufficiently large, the inhibitory action of SC 15396 can be counteracted.

Summary

A new preparation, SC 15396, which inhibits gastrin-stimulated gastric secretion in the dog and rat is described. The material is effective both orally and parenterally in the dog.

Insulin-stimulated secretion in the dog is also inhibited by intravenous injection of the compound.

Its inhibitory effect on histamine-stimulated secretion is much less marked than on gastrin-stimulated secretion, but can be demonstrated most easily on dogs with denervated pouches.

The observations presented here cast doubt on the claim that SC 15396 is a specific antagonist to gastrin.1

The authors are indebted to Dr B. J. Harlow of G. D. Searle & Co. Ltd for supplies of SC 15396.

Requests for reprints should be sent to I. B. Macleod, Department of Clinical Surgery, University of Edinburgh Medical School.

REFERENCES


1Since this article was accepted for publication Bedi and his colleagues have modified their view that SC 15396 is a specific gastrin antagonist (G. Gillespie, V. I. McCuskcr, B. S. Bedi, H. T. Debas, and I. E. Gillespie (1968). Further experimental observations on the gastric acid secretion inhibitor SC 15396. Gastroenterology, 55, 81-87).


Effects of SC 15396 on gastric secretion. 3. The action in the rat.

C G Thomson and W Sircus

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