

Effects of SC 15396 on gastric secretion

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A new compound, 2-phenyl-2-(2-pyridyl) thioacetamide (Fig. 1) with a powerful inhibitory effect on gastric secretion has recently been synthesised.¹ Bedi, Gillespie, and Gillespie (1967), using vagally innervated and Heidenhain pouch dogs, have shown it to inhibit gastrin-stimulated acid secretion. In that they failed to demonstrate any effect on histamine-stimulated or amechol-stimulated gastric secretion, they claim that it is a specific gastrin antagonist.

The compound has a molecular weight of 228.3 and melting point of 133 to 141°C. It is almost insoluble in water, sparingly soluble in petroleum ether, ethanol and propylene glycol, but readily soluble in chloroform and acetone or dimethyl sulphoxide. In preliminary testing it has been shown to have a low acute and chronic toxicity in rats and dogs.

Because of its theoretical and practical potential, we have assessed its effect on gastric secretion stimulated in various ways. The three papers presented here report work undertaken independently,

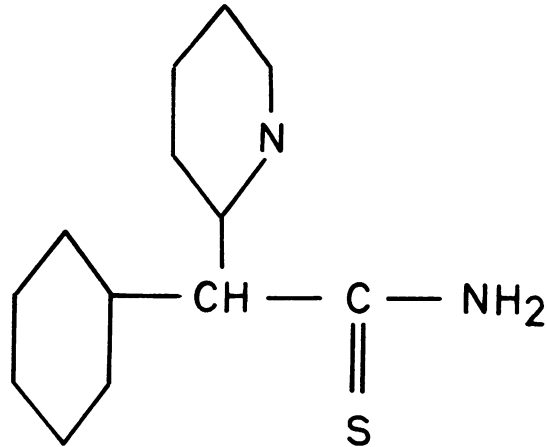


FIG. 1. Formula of SC 15396.

but in view of their complementary findings they are presented and discussed together.

Part I Inhibition of canine gastric secretion by compound SC 15396 given orally and parenterally

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METHODS

Tests were performed on adult greyhound bitches prepared with total gastric fistula. No tests were begun less than six weeks after operation.

Gastric juice was collected by passing an FG.16 Levin tube with multiple openings through the cannula into the stomach and applying suction at -3 to 5 mm mercury, interrupting the suction frequently to apply syringe suction. To test the completeness of recovery, water containing a known concentration of phenol red as a

marker was passed into the stomach via an oral tube and after two minutes was aspirated. In four experiments a mean of 87% of the administered water was recovered.

In earlier studies SC 15396 was administered intravenously in a single dose of 20 mg (1 mg/kg) dissolved in 2 ml of dimethyl sulphoxide (DMSO) but when it became apparent that the material was orally active, direct introduction of a suspension into the stomach became the route of choice. The suspension in water was flushed through the tube with a further 50 ml of water. The cannula was sealed off and no acid withdrawn for one hour subsequently, when no crystals of SC 15396 were recovered in the gastric collection. Gastric juice was

¹SC 15396 synthesised by Dr H. W. Sause of G. D. Searle & Co. Ltd.

stimulated by the gastrin-like pentapeptide, pentagastrin, by histamine, or by insulin.

INTRAVENOUS INJECTION OF SC 15396 The effect of single intravenous injections of 20 mg SC 15396 was studied in two dogs during constant intravenous infusion of pentagastrin (15 $\mu\text{g/hr}$) in two studies and of histamine acid phosphate (1 mg/hr) in a further two studies in each dog.

INTRAGASTRIC SC 15396 AND SUBCUTANEOUS PENTAGASTRIN, HISTAMINE, AND INSULIN The effect of intragastric SC 15396 on the acid response to a subcutaneous injection of pentagastrin was investigated in four dogs each of which was studied three times. A suspension of SC 15396 (20 mg/kg body weight) was placed in the stomach one hour before administration of a single subcutaneous injection of pentagastrin in a dose of 5 $\mu\text{g/kg}$. As control, a similar study, using the same dose of pentagastrin but without prior administration of SC 15396, was done on each occasion.

In similar studies the effect of prior intragastric infusion of SC 15396 on the acid response to histamine acid phosphate and to insulin was examined. Histamine acid phosphate was injected subcutaneously in a dose of 0.2 mg/kg body weight in 12 experiments in four dogs and soluble insulin given subcutaneously in a dose of 0.2 U/kg in four studies in two dogs.

INTRAGASTRIC SC 15396 AND CONSTANT INFUSION OF PENTAGASTRIN The effect of intragastric SC 15396 on the maximal acid response previously established by constant infusion of pentagastrin was studied in 16 experiments in two dogs. In this study, maximal acid secretion was maintained by constant infusion of pentagastrin at a dose of 0.066 $\mu\text{g/kg/minute}$. After the collection of four 15-minute samples of peak acid output, SC 15396 was placed in the stomach and collections were stopped for one hour while the pentagastrin infusion was maintained. Subsequently, suction was recommenced and further four 15-minute samples were obtained. Doses of 20 mg/kg, 10 mg/kg, and 5 mg/kg body weight of SC 15396 were each used four times. In four control studies there was no effect on the acid response following the one-hour period without gastric suction.

RESULTS

EFFECT OF INTRAVENOUS SC 15396 ON GASTRIC JUICE STIMULATED BY A CONSTANT INFUSION OF PENTAGASTRIN In each of four studies a single intravenous injection of 20 mg (1 mg/kg) of SC 15396 resulted in a prompt and marked decrease in acid secretion (Fig. 2). DMSO by itself did not inhibit acid secretion.

EFFECT OF INTRAVENOUS SC 15396 ON GASTRIC JUICE STIMULATED BY A CONSTANT INFUSION OF HISTAMINE Again, in four studies there was an immediate reduction in acid secretion following a single injec-

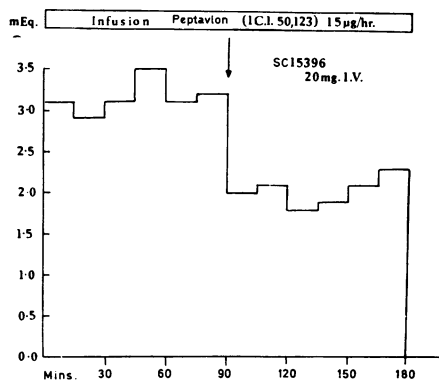


FIG. 2. Effect of a single intravenous injection of 20 mg SC 15396 on acid secretion stimulated by a constant infusion of pentagastrin. The acid output in the hour following SC 15396 differs from that of the hour before injection ($0.01 > p > 0.001$).

tion of 20 mg SC 15396 but it was less marked and of shorter duration than that obtained when gastric juice was stimulated by pentagastrin (Fig. 3), and could have occurred by chance.

EFFECT OF INTRAGASTRIC SC 15396 ON THE ACID RESPONSE TO A SUBCUTANEOUS INJECTION OF PENTAGASTRIN GIVEN ONE HOUR SUBSEQUENTLY In each of 12 studies there was a marked suppression of the acid response to pentagastrin following intragastric administration of SC 15396 (20 mg/kg) as compared with the normal response (Fig. 4). Considering all the tests the mean output of acid in the 90 minutes

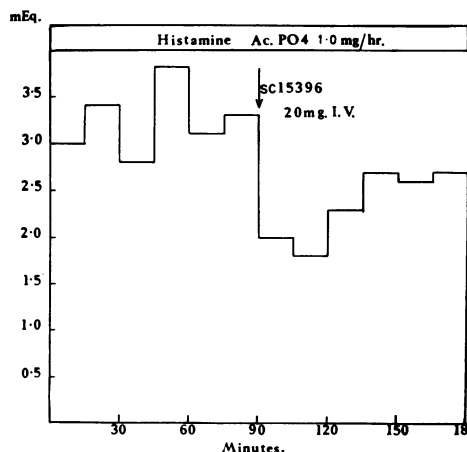


FIG. 3. Effect of a single intravenous injection of 20 mg SC 15396 on acid secretion stimulated by a constant infusion of histamine acid phosphate. These differences in secretion in the hours before and after injection could have occurred by chance ($p > 0.05$).

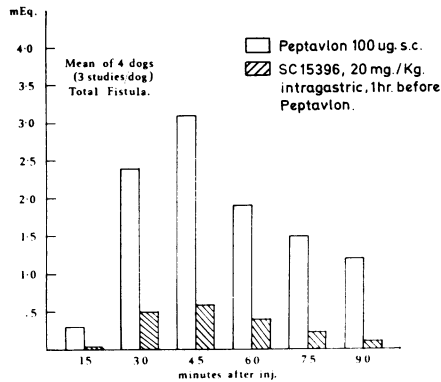


FIG. 4. Effect of intragastric SC 15396 on acid secretion stimulated by subcutaneous pentagastrin. The acid secretion after SC 15396 is lower than the control output using pentagastrin alone ($P < 0.001$).

following injection of SC 15396 was 85% less than that of the control experiment using pentagastrin alone.

EFFECT OF INTRAGASTRIC SC 15396 ON THE ACID RESPONSE TO A SUBCUTANEOUS INJECTION OF HISTAMINE GIVEN ONE HOUR SUBSEQUENTLY Intragastric administration of SC 15396 in a dose of 20 mg/kg failed to prevent the acid response to a maximal stimulus of histamine acid phosphate given one hour subsequently (Fig. 5).

EFFECT OF INTRAGASTRIC SC 15396 ON THE MAXIMAL ACID RESPONSE TO A CONSTANT INFUSION OF PENTAGASTRIN SC 15396 reduced markedly the acid response previously established by a constant infusion of pentagastrin. Each dose used produced

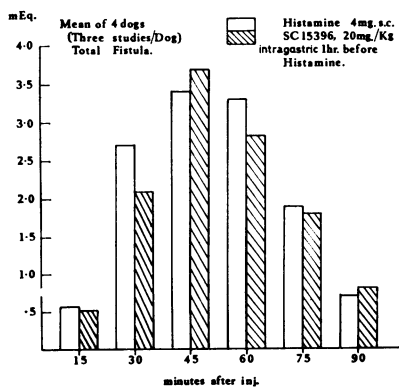


FIG. 5. Effect of intragastric SC 15396 on acid secretion stimulated by subcutaneous histamine acid phosphate.

a mean reduction in gastric secretion: 89% at 20 mg/kg, 68% at 10 mg/kg, and 57% at 5 mg/kg body weight. These results are plotted in Fig. 6 and it will be seen that over the range studied there is apparently a linear relationship between the dose of SC 15396 and reduction in acid secretion achieved. Control experiments where water only was introduced through the cannula showed no reduction in acid secretion over the test period.

When submaximal pentagastrin stimulation was employed (0.0075 μ g/kg/min, a dose of 10 mg/kg SC 15396 effected a reduction in acid secretion of 85% and an intragastric dose of 1 mg/kg a reduction of 33%.

EFFECT OF INTRAGASTRIC SC 15396 ON THE ACID RESPONSE TO A SUBCUTANEOUS INJECTION OF INSULIN In all experiments there was a significant reduction

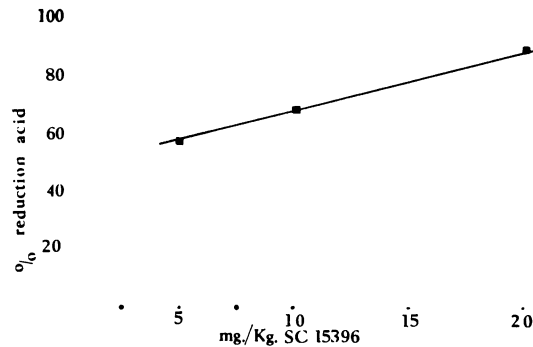


FIG. 6. Effect of intragastric SC 15396 on acid secretion stimulated by insulin. The acid output after SC 15396 is lower than in the control study using insulin alone ($P < 0.001$).

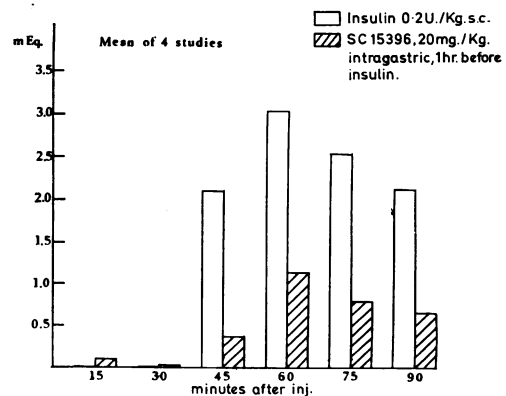


FIG. 7. The effect of different doses on reduction of acid secretion stimulated by a constant infusion of pentagastrin.

in the acid output to insulin. In these four experiments the reduction averaged 66% (Fig. 7).

COMMENT

A gastric fistula provides a collecting system free of the uncertainties inherent in all pouch preparations whether partially innervated or not. The particular procedure employed here is closely related to that used in human studies and allows a very complete recovery of gastric juice. In this particular model SC 15396 has been shown to be a potent inhibitor of gastric juice stimulated by pentagastrin and insulin.

Part II Inhibitory effect of SC 15396 on stimulated canine gastric secretion after surgical procedures

I. B. MACLEOD AND R. A. HILL

METHODS AND MATERIALS

Eight dogs were used in the study, two of each of the following preparations being made: (a) gastric fistula, using a stainless steel cannula; (b) complete antrectomy with gastroduodenal anastomosis, a fistula being made from the residual stomach using a similar cannula to (a); (c) Heidenhain pouch (vagally denervated); and (d) Pavlov pouch (vagally innervated).

Gastric secretion was stimulated in the conscious animal by intravenous infusion of gastrin II, 0.5 $\mu\text{g}/\text{kg}/\text{hr}$; intravenous injection of soluble insulin, 0.15 U/kg, under cover of a constant infusion of KCl (0.5 m-equiv/kg/hr); and by intravenous infusion of histamine acid phosphate 2.0 mg/hr (= 90 to 115 $\mu\text{g}/\text{kg}/\text{hr}$).

SC 15396 was administered either intravenously or orally. For intravenous injection SC 15396 was dissolved in 1 ml of dimethylsulphoxide (DMSO) and 1 ml of saline. For oral administration SC 15396 was mixed in a pellet of bread, which the animal swallowed.

Pilot experiments indicated that 0.5 mg SC 15396 intravenously had no effect on gastrin-stimulated secretion, and that 5 mg had a variable effect. Therefore 50 mg was selected as the standard intravenous dose of SC 15396 to be employed in the main body of experiments. As dogs of different weights were used, this gave a dose range of 2.2 to 4.2 mg/kg body weight. For oral administration a higher dose range was used: standard doses of either 100 mg or 200 mg SC 15396 were given (4.4 to 12 mg/kg body weight). These higher doses were used for oral administration when it became apparent that 50 mg intravenously had little effect on histamine-stimulated secretion.

Acid output was determined on serial 15-minute samples by titration against N/10 NaOH. For the majority of estimations an endpoint of pH 7 was deter-

SUMMARY

SC 15396 in a single intravenous injection depresses the acid response to pentagastrin infusion but has a less marked effect on the response to histamine infusion.

Given orally it significantly inhibits the response to a subcutaneous injection of pentagastrin but not of histamine. It also significantly depresses the acid response to insulin.

Intra-gastric SC 15396 also depresses the acid secretion previously established by the infusion of pentagastrin.

mined, employing an automatic titrator (Radiometer titrator TTT 1c and Autoburette type ABU 1b). For the remainder the endpoint was determined using phenol red (pH 6.8 to 8.4) as an indicator.

In the infusion experiments using either gastrin II or histamine acid phosphatase, a plateau of secretion was achieved before administration of SC 15396, except in the experiment designed to study delayed appearance of secretion following SC 15396. The plateau secretion rate (m-equiv HCl/15 min) during the 45 to 60 minutes before administration of SC 15396 was taken as a control value. In the post-SC 15396 period the mean secretion rate (m-equiv HCl/15 min) was calculated for 30-minute periods and compared with plateau secretion rates to determine the degree and significance of inhibition achieved by SC 15396.

RESULTS

CONTROL STUDIES Each animal was observed for evidence of toxic side effects by observations of pulse rate, rectal temperature, restlessness or drowsiness, and evidence of excessive salivation following oral (200 mg) and intravenous (50 mg) SC 15396. No significant alterations of these parameters were noted during three-hour observation periods.

Intravenous injection of 2 ml of a mixture of DMSO and saline (1 ml of each) did not result in an increase in basal secretion, nor did it exert any significant effect on established secretion stimulated by gastrin, histamine, or insulin. Oral administration of a small bread pellet (the vehicle used to