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Effects of oral calcium gluconate on gastric acid secretion and serum gastrin concentration in man

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SUMMARY A single oral dose of 4·46 mmol calcium gluconate at pH 5·6 was administered intragastrically to 15 male volunteers without gastrointestinal disease. There was a significant rise in acid output from 30-90 minutes after the calcium was given compared with the basal hourly collection. The serum gastrin level 30 minutes after calcium administration was significantly raised, but no correlation could be demonstrated between the acid and gastrin responses. Serum calcium levels were unchanged throughout. An equimolar dose of magnesium sulphate had no such effects. This study suggests that the intragastric administration of calcium results in independent release of gastric acid and gastrin from the gastric mucosa.

Intravenous infusion of calcium chloride has been shown to stimulate gastric acid secretion (Barreras, 1970) and a gastrin response (Reeder *et al.*, 1970; Passaro *et al.*, 1972; Reeder *et al.*, 1974). Although these effects are reproduced by orally administered calcium carbonate, the acid secretory response to this alkaline substance is more pronounced than that of the other alkalis which do not contain calcium (Breuhaus *et al.*, 1950; Fordtran, 1968; Barreras, 1973; Levant *et al.*, 1973). Recently, some workers have shown that the intragastric infusion of calcium chloride, even at an acid pH, stimulated gastric acid secretion (Holtermuller *et al.*, 1974). However, serum gastrin concentration was not altered during these investigations.

This study was undertaken to define the effect of the ingestion of a neutral calcium salt on gastric acid production and serum gastrin concentration in man. The acid and gastrin response to a single oral dose at neutral pH of calcium gluconate or magnesium sulphate was assessed.

Method

SUBJECTS

Twenty-three healthy male volunteers aged between 20 and 30 years of age and with no history of dyspepsia were studied. They were divided into three groups for the three parts of this investigation. Approval for the study was given by the Ethical Committee of Stobhill General Hospital and informed consent was obtained from all subjects.

TESTS

Group 1

Fifteen subjects were studied. The volunteers fasted overnight. In the morning a nasogastric tube was passed into the stomach and its position checked using the water recovery test (Hassan and Hobsley, 1970). Unstimulated gastric acid secretion was collected by continuous suction by means of an electric pump for four 15-minute periods and the aspiration was then stopped. Two grams of calcium gluconate were instilled into the stomach through the nasogastric tube (Injection calcium gluconate B.P. containing 4·46 mmol calcium gluconate in 21 ml distilled water, pH 5·6). After 30 minutes the stomach was emptied by manual suction and continuous gastric aspiration was continued for another four 15-minute periods. Blood samples were obtained by separate venepuncture from a peripheral vein after the nasogastric tube was passed as well as before and 30, 60, and 90 minutes after the intragastric instillation of calcium gluconate. Serum gastrin was assayed in all these samples. Serum calcium was measured in the samples from

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10 of the 15 subjects, while plasma glucose was estimated in the samples from four other subjects.

Group 2
Four subjects were studied; the procedure was similar to that of group 1 except that more frequent blood samples were obtained. An Argyle Medicut catheter was inserted into a peripheral vein and blood samples for the measurement of serum gastrin were obtained at −10, −5, 0, 5, 10, 20, 30, 45, 60, 75, and 90 minutes after calcium gluconate was administered through the nasogastric tube.

Group 3
Four other subjects were studied; the procedure was identical with that of group 1 except that instead of calcium gluconate, magnesium sulphate (4·46 mmol magnesium sulphate in 21 ml distilled water, pH 5·6) was instilled into the stomach through the nasogastric tube.

Techniques

The volume of each gastric aspirate was measured and the acid concentration determined by titration against 0·1 M sodium hydroxide with phenol red as the indicator. Acid output was calculated for the control 60-minute period and the hour between 30 and 90 minutes after calcium gluconate or magnesium sulphate administration.

Plasma glucose estimations were performed using the autoanalyser method of Trinder (1969). The clotted blood samples were centrifuged and the sera separated and stored at −20°C. Calcium concentration was determined by a fluorimetric technique using a Corning-EEL model 940 calcium analyser. Serum gastrin was measured by the radioimmunoassay method of Ganguli and Hunter (1972). Natural porcine gastrin I was used for radio-iodination and natural porcine gastrin II (MRC Research Standard 66/138) was the standard. Each serum sample was assayed in duplicate at three dilutions and the mean coefficient of variation for this study was 7% (range: 2-11%). The mean serum gastrin concentration obtained from the six replicates was used. The results were analysed using Student's *t* test for paired values and correlations obtained by application of linear regression.

Results

GROUP 1
The mean acid output during the hour 30-90 minutes after the intragastric instillation of calcium gluconate was significantly greater than during the control hour ($P < 0.005$). Although the greatest response occurred during the first 15-minute period collected (Fig. 1), the effect was still present

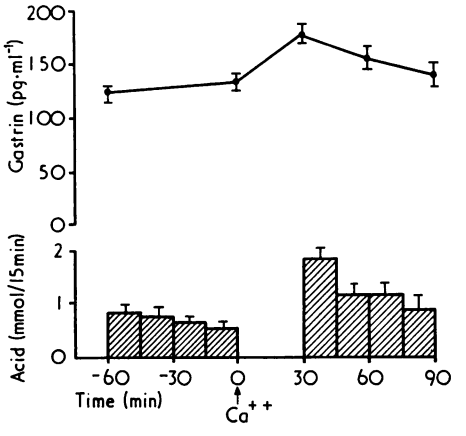

Fig. 1 *Acid output and serum gastrin concentration before and after the intragastric instillation of calcium gluconate (4·46 mmol in 21 ml distilled water).* ▨: *acid output (mean ± SE);* Ca^{++}: *time when calcium gluconate was given;* ⧫: *serum gastrin concentration (mean ± SE).*

during the fourth 15-minute period in six of the 15 subjects studied. There was no increase in gastric acid output after the administration of calcium gluconate in four of the 15 volunteers.

The mean serum gastrin concentration after nasogastric intubation was greater than before intubation but this difference was not statistically significant. There was a significant increase in the mean serum gastrin concentration at 30 minutes ($P < 0.001$) and 60 minutes ($P < 0.025$) but not 90 minutes after calcium gluconate, compared with the mean control value obtained before nasogastric intubation. When the mean serum gastrin concentration during the post-intubation control period was compared with the mean values after calcium gluconate, only the raised level at 30 minutes reached statistical significance ($P < 0.005$). In three of the 15 subjects there was no increase in serum gastrin concentration after the administration of calcium gluconate; two of these three subjects were the same as two of the four volunteers in whom there was no alteration in gastric acid output after calcium gluconate.

There was no significant correlation between acid output and serum gastrin concentration either during the control period ($P > 0.4$) or the 15-minute period of peak acid output and the peak gastrin concentra-

tion ($P > 0.2$) nor was there a significant correlation between the rise in serum gastrin level and the rise in acid secretion ($P > 0.6$). As gastrin stimulates acid release, we attempted to correlate the gastrin levels after the calcium was instilled with the 15-minute acid collections obtained thereafter. Once again no significant correlation was demonstrated. There was no significant alteration in plasma glucose or serum calcium concentration in any of the subjects studied.

GROUP 2

Figure 2 shows the time course of the serum gastrin

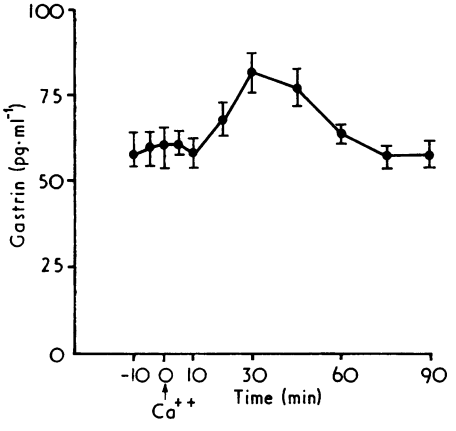

Fig. 2 *Time-course of the change in serum gastrin concentration after calcium gluconate.* ⊕ *: mean ± SE.*

response to the intragastric instillation of calcium gluconate. Serum gastrin concentration was markedly raised at 20 minutes ($P < 0.05$), 30 minutes ($P < 0.001$), and 45 minutes ($P < 0.05$) after calcium gluconate; the response was over by 60 minutes. There was no significant difference between the mean serum gastrin concentration of the three samples taken before and five and 10 minutes after the administration of calcium gluconate. This gastrin response to intragastric calcium gluconate was noted in all the four subjects studied.

GROUP 3

There was a decrease in the mean acid output after magnesium sulphate but this was not statistically significant. There was no change in serum gastrin concentration after this drug (Fig. 3). These findings were observed in each of the four subjects studied.

Discussion

Our study demonstrates the ability of a single dose

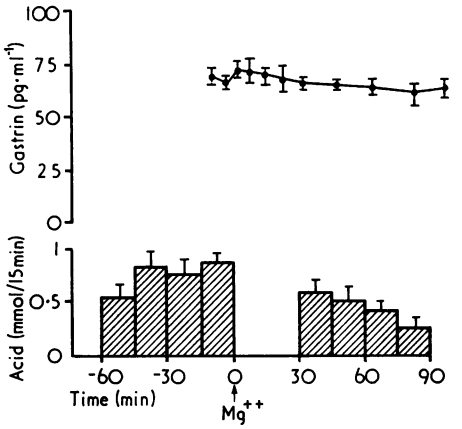

Fig. 3 *Acid output and serum gastrin concentration before and after the intragastric instillation of magnesium sulphate (4·46 mmol in 21 ml distilled water).* ▨ *: acid output (mean ± SE); Mg^{++}: time when magnesium sulphate was given;* ⊕ *: serum gastrin concentration (mean ± SE).*

of intragastric calcium gluconate in distilled water to increase acid output and serum gastrin concentration without the production of hypercalcaemia. The change in the acid secretion rate did not significantly correlate with the mean or peak change in serum gastrin level over the same period, nor was there any significant correlation between the peak serum gastrin concentration and the peak acid response in the individual subject. It seems likely, therefore, that the acid and gastrin responses are independent, although the design of the study does not preclude a significant correlation in the first 30 minutes after the calcium was given when acid was not collected. These observations suggest that calcium ions have specific effects on gastric acid and endogenous gastrin secretion and that the sites of these actions may be local. Recently it was suggested that calcium ions may act as coupling factors between excitation and secretion in exocrine and endocrine glands (Rasmussen, 1972). These actions were likely to be mediated by the activation of the cyclic AMP system (Rubin *et al.*, 1972). Similar mechanisms may be operative at the gastrin and parietal cell level. This is quite probable as there is increasing evidence that cyclic AMP may be the universal mediator of gastric acid secretion (Fromm *et al.*, 1975; Katsumata and Glick, 1975).

The acid and gastrin responses to oral calcium are small compared with the other known stimulants (Holtermuller *et al.*, 1974). Again, there is no reported difference in the clinical effectiveness of calcium-containing antacids as compared with those

antacids which do not contain calcium. Calcium salts have been used in the treatment of the malabsorption syndrome, osteoporosis, and hypoparathyroidism for several decades and yet there are no reports of an increased incidence of peptic ulceration in these conditions. Thus there seems to be little evidence for a clinical relevance for these observations of the increased acid and gastrin responses to orally administered calcium ions. This may be because the link between gastric acid output, serum gastrin concentration and peptic ulceration, with the exception of gastrinomas, remains tenuous. On the other hand, Grossman (1974) recently showed that milk has a gastric acid-stimulating effect in rats and that this is abolished when 90% of the calcium is replaced by sodium. This observation suggests that the possible clinical effects of a regular intake of calcium salts, whether for a therapeutic purpose or taken as milk, merit further study in patients with and without peptic ulcer disease.

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