Interaction of calcium and pentagastrin on gastric acid secretion in man

J. CHRISTIANSEN AND L. HENDEL

From the Department of Surgical Gastroenterology, Glostrup Hospital, Copenhagen, Denmark

SUMMARY In a recent report based on the study of a single human subject calcium was found to potentiate the action of pentagastrin on gastric acid secretion.

To elucidate this problem gastric acid secretion was studied in five patients during stimulation with pentagastrin and during stimulation with pentagastrin and calcium. No potentiation between the two agents was found.

The stimulation of gastric acid secretion in man in response to intravenous infusion of calcium has been reported by several investigators (Donegan and Spiro, 1960; Fillastre, Blaise, Bernier, and Richet, 1963; Murphy, Goldstein, Boyle, and Ward, 1966; Barreras and Donaldson, 1967). The magnitude of the calcium-induced acid secretion in duodenal ulcer patients amounts to approximately 30% of the maximum response to betazole hydrochloride (Murphy *et al*, 1966; Barreras and Donaldson, 1967). The mechanism by which calcium induces gastric secretion is not clear, but recent studies have shown that calcium is able to produce a release of gastrin (or decreased destruction) (Trudeau and McGuigan, 1969; Isenberg, Walsh, Passaro, and Grossman, 1972). It has also been shown, however, that calcium infusion can produce increased acid secretion in patients who have had a truncal vagotomy and antrectomy which suggests a direct stimulation of the parietal cells (Basso and Passaro, 1970).

This observation renders probable that the interaction of calcium and gastrin consists not only in a release of gastrin but also in a potentiation of gastrin by calcium. Basso and Passaro (1970) actually found that calcium potentiates the action of pentagastrin on acid secretion in ferrets, and the study of a single human subject also showed that potentiation occurred.

The motive for the present study has been a more thorough investigation of this latter observation.

Materials and Methods

The material comprises five patients, two men and

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three women, their ages ranging from 30 to 59 years. Two of the patients had a duodenal ulcer, and three cholelithiasis. The consent of the patients was obtained after explanation of the studies involved.

Each patient was examined twice on separate days. The position of the Levine tube was ascertained by fluoroscopy. The collection of gastric juice was effected by intermittent mechanical suction (Egnell pump) with a partial vacuum of 150 mm mercury. A marker substance was instilled into the stomach through a thin tube welded to the Levine tube (^{51}Cr -EDTA, flow 45 ml/hr) in order to determine recovery.

The volume of the secretion was measured for each 15-minute period and the concentration of H^+ was determined by titration with an autotitrator (Radiometer, Copenhagen) to pH 7.0, and the concentration of ^{51}Cr -EDTA was determined in a well counter. The volume of the secretion collected and the output of H^+ was corrected as to the actual recovery by way of the marker substance instilled.

The concentration of calcium in serum was determined by atomic absorption spectrophotometry. All infusions were carried out by means of constant infusion pumps (Braun-Melsungen unit).

In the first test the basal secretion was collected for two 15-minute periods. This was followed by continuous intravenous infusion of pentagastrin, $1.5 \mu\text{g/kg-hr}$ for two hours. This submaximal dose of pentagastrin results in a steady-state secretion (Nordgren, 1971).

In the second test, which was carried out as described above, a continuous intravenous infusion of calcium gluconate ($4 \text{ mg Ca}^{++}/\text{kg-hr}$) was added. The calcium infusion was begun at the same time as

the pentagastrin infusion and continued for two hours. Venous blood samples for determination of the calcium concentration was taken at the start of the pentagastrin infusion, 30 minutes later, and then at intervals of 15 minutes.

For the statistical evaluation of the results Student's *t* test was applied (Snedecor and Cochran, 1967).

Results

Mean basal acid output was 5.1 m-equiv/hr.

Figure 1 shows the mean serum calcium concentration during steady-state secretion in the second hour of stimulation with pentagastrin and with pentagastrin and calcium respectively. In all cases a significant increase in serum calcium concentration occurred ($P < 0.05$).

Figure 2 shows the acid output during steady-state secretion in the second hour of stimulation with pentagastrin and with pentagastrin and calcium respectively. In all cases a slight but non-significant decrease in acid output occurred ($P > 0.10$). This is also illustrated in Fig. 3, which shows the mean acid

output (m-equiv H^+ /15 min) in the four 15-minute periods of steady-state secretion for all patients. The acid output during simultaneous infusion of pentagastrin and calcium was on a lower level than during infusion of pentagastrin alone, but, as can be seen from the confidence limits, there is no significant difference between the two secretory levels.

The mean acid output during steady-state secretion for all patients was 35.9 m-equiv/hr (SD:8.1) during infusion of pentagastrin and 32.4 m-equiv/hr (SD:14.1) during infusion of pentagastrin and calcium.

Discussion

Observations in patients with the combined Zollinger-Ellison syndrome and primary hyperparathyroidism suggest that calcium is able to produce a release of gastrin (Trudeau and McGuigan, 1969; Isenberg *et al*, 1972). These authors have reported two patients with the combination of parathyroid adenoma/hyperplasia and a gastrinoma in whom removal of the parathyroid adenoma or hyperplastic parathyroid glands resulted in a marked decrease in blood gastrin

Fig. 1

Fig. 1 Mean serum calcium concentration during steady-state secretion in each patient after stimulation with pentagastrin and after stimulation with pentagastrin and calcium.

Fig. 2

Fig. 2 Acid output during steady-state secretion in each patient after stimulation with pentagastrin and after stimulation with pentagastrin and calcium.

Fig. 3 Mean acid output (all patients) during steady-state secretion after stimulation with pentagastrin and after stimulation with pentagastrin and calcium (means ± 2 SE).

which could be restored to preoperative levels by calcium infusion. A similar observation was reported by Basso and Passaro (1970) who in addition studied the effect of calcium infusion in four patients with the Zollinger-Ellison syndrome but without hyperparathyroidism. Calcium was an uniquely potent stimulus of acid secretion in these patients. The maximum response to calcium stimulation equalled or exceeded in each instance the maximum response to betazole hydrochloride.

A significant increase in serum gastrin levels during calcium infusion has also been demonstrated in duodenal ulcer patients and in normal controls (Reeder, Jackson, Ban, Clendinnen, Davidson, and Thompson, 1970).

These studies show that calcium can produce a release (or decreased destruction) of gastrin.

The observation by Basso and Passaro (1970) that calcium is able to potentiate the action of pentagastrin in man (based on the study of one subject) is in contrast to the results of the present study. This discrepancy is presumably not due to differences in the doses of pentagastrin and calcium used. In our study a submaximal dose of pentagastrin of 1.5 µg/kg-hr was used compared with 3 µg/kg-hr in the study of Basso and Passaro while the total amount of Ca⁺⁺ administered was almost the same (8 mg versus 7.5 mg).

Of more importance is that all five patients in our study showed the same secretory pattern, ie, a slightly decreased acid secretion during stimulation with pentagastrin and calcium compared with stimulation with pentagastrin alone. This is incompatible with the concept that calcium potentiates pentagastrin-induced gastric acid secretion in man at these dose levels. The significance of the lower acid response to the combined infusion of pentagastrin and calcium is doubtful.

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