

Effect of metiamide on basal and stimulated serum cholecystokinin levels in duodenal ulcer patients

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SUMMARY Serum cholecystokinin (CCK) levels were measured in 10 patients with chronic duodenal ulcers, fasting and at intervals after two standard test meals (300 ml of 40 mmol/l phenylalanine solution), one given before and one during H₂-receptor blockade with metiamide (200 mg four times a day). Fasting serum CCK levels were lower in all patients during treatment with metiamide (the mean level falling from 306.0 ± 102.0 (SEM) to 82.1 ± 23.6 pg/ml after treatment (P < 0.01)). In contrast, peak serum CCK levels after the meal were not significantly different (7400 ± 1141 pg/ml before treatment and 7569 ± 1293 pg/ml on metiamide). We conclude that in duodenal ulcer patients CCK secretion under basal conditions may be in part dependent on stimulation of the small intestinal mucosa by gastric acid, but that, after an amino acid meal, gastric acid secretion is less important in determining the amount of CCK released.

Acid is a known stimulus for CCK release under experimental circumstances (Wang and Grossman, 1951; Berry and Flower, 1971; Wormsley, 1971; Konturek *et al.*, 1974; Barbezat and Grossman, 1975), but the relative importance of this effect in physiological situations is still somewhat uncertain. Previous studies have all recorded the effects of introducing acid into the small intestine. As an alternative approach, we have studied the effect on serum CCK of decreasing endogenous gastric acid secretion by histamine H₂-receptor blockade with metiamide (Black *et al.*, 1973; Mainardi *et al.*, 1974; Milton-Thompson *et al.*, 1974; Celestin *et al.*, 1975) in patients with chronic duodenal ulceration.

Methods

The studies were carried out in 10 patients, who were taking part in an open trial of metiamide in chronic duodenal ulcer disease. After an overnight fast a nasogastric tube was passed and screened into position in the antrum. The stomach contents were aspirated and an aliquot retained for pH measurement. A test meal consisting of 300 ml of 40 mmol/l phenylalanine was then warmed to 37°C and delivered rapidly through the nasogastric tube. Small (10 ml) samples of gastric contents were aspirated at fixed intervals (10, 20, 30, 45, 60, 90,

and 120 minutes) after the test meal, and returned to the stomach after measurement of their pH by an automatic pH meter (Radiometer, Copenhagen). Blood samples were obtained *via* an indwelling intravenous cannula, fasting and at the same intervals as the gastric aspirates, and after separation the serum samples were stored at -20°C. After the initial test meal, treatment with metiamide, 200 mg four times a day, was started and continued for at least two months (64 ± 4.7 days). A second test meal was then given in exactly the same way as before, except that on this occasion an oral dose of metiamide 200 mg was given in 25 ml water one hour before the start of sampling. The CCK levels in all the serum samples from the whole study were later measured in the same batch by radioimmunoassay (method published in detail—Harvey *et al.*, 1974a), and expressed as serum CCK-like immunoreactivity in terms of a CCK-33 standard derived from highly purified hormone (batch of 11-11-1970) supplied by Professor V. Mutt. Because at least two varieties of CCK are present in the body (Mutt and Jorpes, 1968; Debas and Grossman, 1973; Harvey *et al.*, 1974b) and are measured by this assay to differing degrees, and because no standard preparation of CCK is currently available, it is not at present possible to give absolute figures for CCK levels in tissues or serum when using this assay, and, as with other radioimmunoassays for which properly evaluated standard preparations are not available,

all figures should be regarded as relative rather than absolute (Harvey *et al.*, 1974a). The significance of the differences in CCK levels before and during treatment with metiamide was tested by three different statistical methods—*t* test (parametric), paired *t* test, and Wilcoxon rank test (non-parametric).

Results

Treatment with metiamide produced the expected inhibition of acid secretion, and the mean antral hydrogen ion concentration (derived from antral pH values) was lower at all times after the meal during the period of H₂-receptor blockade. Figure 1 illustrates the mean hydrogen ion concentrations ± SEM before and during treatment. Fasting CCK levels fell in all patients during treatment (mean level falling from 306.0 ± 102.0 (SEM), median 189, picograms per ml to 82.1 ± 23.6, median 57 pg/ml (Wilcoxon rank test: *P* < 0.01) (Fig. 2). In contrast, peak serum CCK levels after the test meal were not significantly altered (7.40 ± 1.14 ng/ml before treatment and 7.57 ± 1.29 ng/ml after metiamide). The average time from ingestion of the meal to the time at which the peak serum CCK level was reached was 34.5 ± 4.3 minutes before treatment and 34.0 ± 3.2 minutes after metiamide. Figure 3 illustrates the mean CCK levels at each sampling time (it does not show the true mean peak values above, as peak values were reached at different times in different individuals). CCK levels at 90 and 120 minutes were also significantly lower during treatment (*P* < 0.01, < 0.02 respectively by all three statistical methods employed).

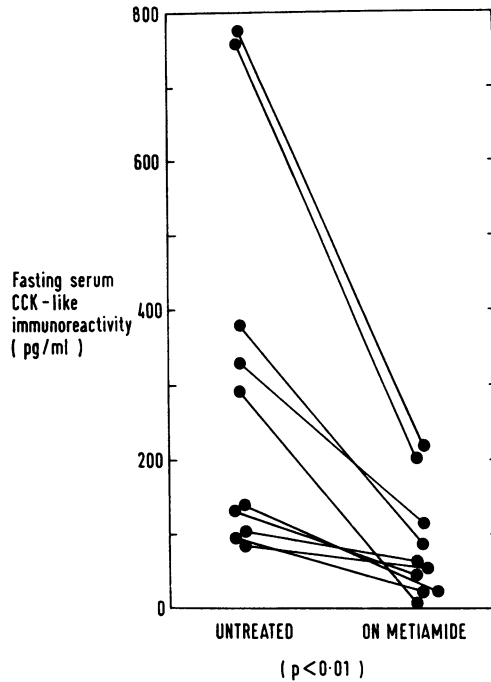


Fig. 2 Fasting serum CCK-like immunoreactivity before and during treatment with metiamide in duodenal ulcer patients.

Discussion

The fact that fasting serum CCK levels fell after H₂-receptor blockade in each of the 10 patients

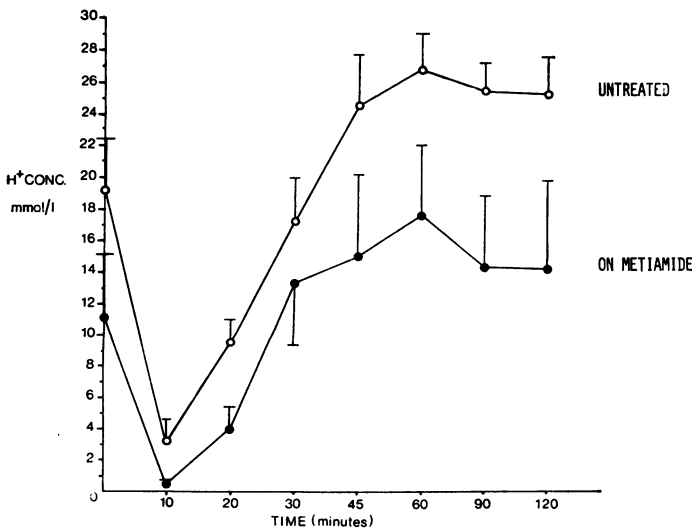


Fig. 1 Hydrogen ion concentrations (mean ± SEM) during test meal in the 10 subjects before treatment and after two months' therapy, with metiamide 0.8 g daily.

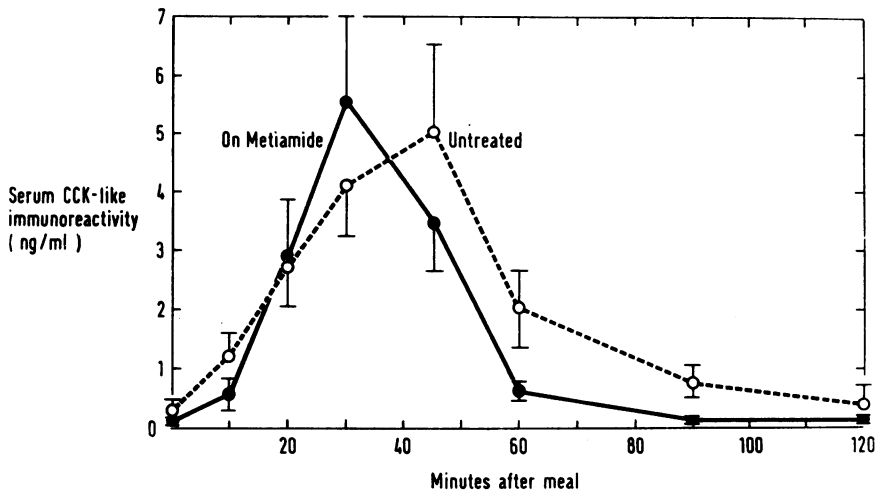


Fig. 3 Serum CCK-like immunoreactivity (mean \pm SEM) in the 10 subjects after the two test meals.

suggests that metiamide may reduce the basal rate of CCK secretion. Other possible explanations—for example, that metiamide increases the rate of metabolism of CCK—seem less likely. A reduction in the rate of CCK secretion might be due to a direct effect of metiamide on the CCK cell, but this also seems improbable, as CCK release after the test meal was not inhibited by metiamide. The finding that fasting serum CCK levels are decreased by metiamide is consistent with the hypothesis that the entry of gastric acid into the duodenum stimulates CCK release under physiological circumstances. Such a mechanism might be expected to be more important in fasting subjects than after food, as after meals the amount of unbuffered acid entering the duodenum is probably not normally enough to stimulate release of significant amounts of CCK (Barbezat and Grossman, 1975). In patients with the Zollinger-Ellison syndrome (Thompson *et al.*, 1973) or pancreatic exocrine deficiency (Harvey *et al.*, 1973) raised fasting serum CCK levels have been found, and in both these conditions the contents of the upper small intestine are more acid than in normal circumstances. The findings of the present study suggest that release of CCK by acid might contribute to the raised serum levels found in such patients, although it is possible that in some patients with the Zollinger-Ellison syndrome the tumour secretes CCK as well as gastrin, as raised plasma levels may be found in such patients even after total gastrectomy (Thompson *et al.*, 1975).

Patients with duodenal ulceration secrete more trypsin than do control subjects, in response to acid in the small intestine (Thjodleifsson and Wormsley, 1975), so the higher fasting CCK levels in untreated duodenal ulcer patients may in part reflect an

increased reactivity of the CCK cell to the action of acid. In this study CCK levels at 90 and 120 minutes were also significantly higher before treatment in conjunction with a significantly higher acidity, perhaps indicating that an increased reactivity of the CCK cell in these patients is again revealed in the later stages of the response to an amino acid meal. Because CCK probably exists in the body in more than one form (Mutt and Jorpes, 1968; Debas and Grossman, 1973; Harvey *et al.*, 1974b), and because the different forms may vary in their half-lives in the blood, a change in the type of CCK secreted by duodenal ulcer patients might occur as a result of treatment with metiamide, and this also could possibly account for the observed changes in fasting serum cholecystokinin levels. Further studies have not been possible, as metiamide has now been withdrawn from use, after reports of transient agranulocytosis (Forrest *et al.*, 1975). However, cimetidine, another H₂-receptor blocking agent, is currently being introduced (Burland *et al.*, 1975; Henn *et al.*, 1975; Spence *et al.*, 1976) and may prove suitable for further studies of the effects of acid on the small intestine.

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