Effect of treatment with cimetidine for one year on gastrin cell and parietal cell function and sensitivity to cimetidine in patients with duodenal or gastric ulcers

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Summary

Twenty-two duodenal and 16 gastric ulcer patients were treated with 400 mg cimetidine twice daily for one year after their ulcers had healed. No change in gastric acid secretion was observed before and after treatment in 20 duodenal and 13 gastric ulcer patients. Similarly, the inhibitory effect of 200 mg cimetidine on gastric acid secretion was unaltered in 11 duodenal and 6 gastric ulcer patients studied and cimetidine blood concentration were unchanged in 9 duodenal and 4 gastric ulcer patients after one year. In 7 duodenal and 6 gastric ulcer patients the serum gastrin response to a standard test meal before and after treatment was identical.

Introduction

Maintenance treatment with cimetidine in a low dose is effective in preventing duodenal ulcer relapse (Bodemar and Walan, 1978; Blackwood, Maudgal and Northfield, 1978; Gumand-Høyer *et al.*, 1978; Burland *et al.*, 1978; Gray *et al.*, 1978; Hetzel *et al.*, 1978). In the prevention of gastric ulcer relapse cimetidine seems equally effective (Machell *et al.*, 1979; Birger Jensen *et al.*, 1979). Treatment with cimetidine for short periods seems to be safe, but after-effects of such treatment on parietal and gastrin producing cells may become overt only during long-term treatment. Furthermore, it has to be demonstrated that inhibition of gastric acid secretion by cimetidine does not change with time. Some of these aspects have been studied in duodenal ulcer patients. (Hetzel *et al.*, 1978; Forrest *et al.*, 1979; Spence *et al.*, 1978a, b; Sewing *et al.*, 1978; Bodemar *et al.*, 1979). In gastric ulcer patients, however, no studies of this kind have yet been done. This study was undertaken to assess the effect of one year's continuous treatment with cimetidine on gastrin-cell function (as determined by postprandial serum gastrin levels) and on parietal cell function (as assessed by basal and pentagastrin-stimulated gastric acid secretion) in duodenal and gastric

ulcer patients. The inhibition of gastric acid secretion by cimetidine was also studied, before and after one year's treatment.

Patients and methods

Thirty-eight peptic ulcer patients without prior gastric surgery were studied, 22 of whom had a duodenal and 16 a gastric ulcer. One duodenal ulcer and 7 gastric ulcer patients were females. The mean age in duodenal ulcer patients was 48 ± 4 years and in gastric ulcer patients, 51 ± 3 years. All patients had endoscopically assessed healed ulcers before the start of maintenance treatment. Treatment with 400 mg cimetidine after breakfast and 400 mg at bedtime was continued for one year. To test patient compliance, a qualitative check on cimetidine in a urine sample was performed at each bi-monthly follow-up visit. The detection of cimetidine in the urine was performed by thin layer chromatography (Smith, Kline and French Laboratories, England; personal communication). Immediately before the start of cimetidine treatment, several tests were undertaken in a number of patients. These tests were repeated one year later between 3 and 7 days after cimetidine had been stopped. At repeat tests for gastric acid secretion and serum gastrin, concomitant blood cimetidine concentrations were assessed: these were all below detection level ($< 0.05 \mu\text{g/ml}$).

Tests performed:

Gastric analysis was done in 20 duodenal and 13 gastric ulcer patients. After an overnight fast, a gastric tube was positioned according to the method described by Hector (1968). Four 15-min basal secretory collections were aspirated and subsequently 4 15-min samples were collected after i.m. injection of $6 \mu\text{g/kg}$ pentagastrin. Peak acid output was calculated as the sum of the 2 consecutive highest 15-min samples multiplied by 2. Hydrogen

ion concentration (mmol H⁺/l) was determined by titration with 0.1 mol NaOH up to pH 7.0.

Gastric acid secretion after cimetidine was determined in 11 duodenal and 6 gastric ulcer patients.

One hour after the oral intake of 200 mg cimetidine, gastric secretion was measured as described above. However, basal secretion was measured during 2 15-min periods only. This 30-min result was multiplied by 2 and expressed as mmol H⁺/hr.

Cimetidine blood concentrations were measured in 9 duodenal and 4 gastric ulcer patients. Venous blood samples were drawn 60, 90, 105 and 135 min after the oral intake of 200 mg cimetidine during gastric analysis. Heparinized whole blood was stored at -20°C and cimetidine concentrations were determined by high pressure liquid chromatography as described by Randolph *et al.*, (1977). The minimal detectable blood concentration by this method was 0.05 µg/ml. All samples were assessed in duplicate.

Serum gastrin levels were measured in 7 duodenal and 6 gastric ulcer patients. Levels were determined, fasting and 15, 30, 45, 60, 90 and 120 min after a standard test meal. The test meal consisted of one slice of white bread, 50 g cheese, one boiled egg and 200 ml skimmed milk, containing in total: 30 g protein, 20 g fat and 24 g carbohydrate. The integrated gastrin response (IGR) was calculated by determining the area under the curve of the gastrin concentrations after subtraction of the basal concentration. Pre-treatment samples were stored at -20°C and were analysed together with post-treatment samples in the same assay to avoid inter-assay variation. Serum gastrin concentrations were assessed by radio-immunoassay using a rabbit antiserum (Rehfeld, Stadil and Rubin, 1972; Lamers, 1976). This antiserum raised against human gastrin I, 2-17, co-valently coupled to bovine serum albumin, binds all known C-terminal gastrin components with an almost equimolar potency (Rehfeld *et al.*, 1979). In 137 normal subjects the serum gastrin concentration was 39 ± 15 pg/ml (mean ± 1 s.d.; range 10-86 pg/ml).

For statistical analyses Wilcoxon's Signed Rank test for matched pairs and Mann Whitney U test were used. Data are presented as the mean ± 1 s.e.mean. Lack of significant differences on statistical analysis is signified by (n.s.).

Results

Patient compliance

No patient failed to attend any of the follow-up visits during maintenance treatment. Bi-monthly urine cimetidine checks were, with 14 exceptions (6%) in different patients, all positive.

Gastric acid secretion and its inhibition by cimetidine

There was no difference between the pre- and post-treatment data neither in duodenal nor in gastric ulcer patients (Figs 1(a) and 1(b)).

Blood cimetidine concentrations

There was no difference between the data of the duodenal and the gastric ulcer patients studied and so they were pooled. The mean cimetidine blood level between 60 and 135 min after oral medication with 200 mg before treatment was 0.83 ± 0.08 µg/ml and after one year 0.88 ± 0.08 µg/ml (n.s.). The mean peak blood concentrations were 1.05 ± 0.10 and 1.11 ± 0.10 µg/ml (n.s.) respectively.

Serum gastrin

In duodenal ulcer patients the fasting and meal-stimulated serum gastrin concentrations before and after one year's treatment were not significantly different; the fasting concentrations being 42 ± 5 and 47 ± 5 pg/ml (n.s.) and the IGR 5.8 ± 0.8 and 6.1 ± 1.4 ng/ml at 120 min (n.s.) respectively. In gastric ulcer patients, the fasting serum gastrin concentration before treatment was 42 ± 7 pg/ml and after therapy 58 ± 11 pg/ml (n.s.). The IGRs were 6.4 ± 1.2 and 7.0 ± 1.3 ng/ml at 120 min (n.s.) (Fig. 2) respectively.

Discussion

The present study shows that one year's treatment with cimetidine does not influence gastric acid secretion. Other investigators reported similar findings in duodenal ulcer patients (Bodemar and Walan, 1978; Forrest *et al.*, 1979; Spence *et al.*, 1978a). This study shows that gastric acid secretion in gastric ulcer patients is also unaltered. Whatever mechanism causes the relative hyposecretion of gastric acid in gastric ulcer patients, it was unchanged after one year's treatment with cimetidine while the ulcer remained healed. The basal and post-prandial serum gastrin concentrations in duodenal and gastric ulcer patients were unaltered after one year's treatment with cimetidine. Other reports on serum gastrin in duodenal ulcer patients after the long-term use of cimetidine have been conflicting (Forrest *et al.*, 1979; Spence *et al.*, 1978b; Sewing *et al.*, 1979). There are no other reports on serum gastrin in gastric ulcer patients after the long-term use of cimetidine.

It might be assumed that possible after-effects of long-term cimetidine treatment on gastrin cell function and on parietal cell function will become manifest earlier in gastric ulcer patients than in duodenal ulcer patients owing to the significantly lower gastric acid secretion after cimetidine in this condition (Festen, Lamers and van Tongeren, 1978). Such an effect, however, was not demonstrated in this study.

FIG. 1. Gastric acid secretion before and after 200 mg cimetidine (mmol H⁺/hr; mean $\pm$ s.e. mean) and resulting percentage inhibition (mean $\pm$ s.e. mean) before (□) and after (▨) one year's treatment with cimetidine.

Cimetidine remained effective during one year's continuous treatment: blood concentrations of cimetidine and inhibition of gastric acid secretion were unchanged.

It is concluded that after one year's maintenance therapy with cimetidine in duodenal and gastric ulcer patients no rebound phenomena, or after-effects on gastric acid secretion, or serum gastrin concentrations were observed. The acid inhibitory effect of cimetidine did not change.

FIG. 2. Serum gastrin levels (pg/ml; mean $\pm$ s.e. mean) fasting and in response to a test meal before ($\bullet$ — $\bullet$) and after one year treatment ($\circ$ — $\circ$) with cimetidine in (a) 7 duodenal and (b) 6 gastric ulcer patients.

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References

- BIRGER JENSEN, K., MÖLLMANN, K.M., RAHBK, I., RASK MADSEN, J., RUNE, S.J. & WULFF, H.R. (1979) Prophylactic effect of cimetidine in gastric ulcer patients. *Scandinavian Journal of Gastroenterology*, **14**, 175.
- BLACKWOOD, W.S., MAUDGAL, D.P. & NORTHFIELD, T.C. (1978) Prevention by bedtime cimetidine of duodenal ulcer relapse. *Lancet*, **i**, 626.
- BODEMAR, G. & WALAN, A. (1978) Maintenance treatment of recurrent peptic ulcer by cimetidine. *Lancet*, **i**, 403.
- BODEMAR, G., NORLANDER, B., FRANSSON, L. & WALAN, A. (1979) The absorption of cimetidine before and during maintenance treatment with cimetidine and the influence of a meal on the absorption of cimetidine. Studies in

patients with peptic ulcer disease. *British Journal of Clinical Pharmacology*, **7**, 23.

- BURLAND, W.L., HAWKINS, B.W., HORTON, R.J. & BERESFORD, J. (1978) The longer-term treatment of duodenal ulcer with cimetidine. In: *Cimetidine: Proceedings of the Westminster Hospital Symposium 1978*. (Ed by Wastell, C. & Lance, P.), p. 66. Churchill-Livingstone, Edinburgh, London and New York.
- FESTEN, H.P.M., LAMERS, C.B.H. & VAN TONGEREN, J.H.M. (1978) De onderdrukking van de maagzuurproductie door middel van cimetidine: resultaten van een dubbelblind onderzoek naar de betekenis van cimetidine voor de behandeling van peptische ulcera. *Nederlandsche Tijdschrift voor Geneeskunde*, **122**, 862.
- FORREST, J.A.H., FETTES, M.R., MCLOUGHLIN, G.P. & HEADING, R.C. (1979) The effect of long-term cimetidine on gastric acid secretion, serum gastrin and gastric emptying. *Gut*, **20**, 404.
- GRAY, G.R., SMITH, I.S., MACKENZIE, I. & GILLESPIE, G. (1978) Long-term cimetidine in the management of severe duodenal ulcer dyspepsia. *Gastroenterology*, **74**, 397.
- GUMAND-HØYER, E., BIRGER-JENSEN, K., KRAG, E., RASK MADSEN, J., RAHBK, I., RUNE, S.J. & WULFF, H.R. (1978) Prophylactic effect of cimetidine in duodenal ulcer disease. *British Medical Journal*, **1**, 1095.
- HECTOR, R.M. (1968) Improved technique of gastric aspiration. *Lancet*, **i**, 15.
- HETZEL, D.J., HANSKY, J., SHEARMAN, D.J.C., KORMAN, M.G., HECKER, R., TAGGART, G.J., JACKSON, R. & GABB, B.W. (1978) Cimetidine treatment of duodenal ulceration. Short-term clinical trial and maintenance study. *Gastroenterology*, **74**, 389.
- LAMERS, C.B.H.W. (1976) *Some aspects of the Zollinger-Ellison syndrome and serum gastrin*. Thesis, Nijmegen University.
- MACHELL, R.J., CICLITIRA, P.J., FARTHING, M.J.G., DICK, A.P. & HUNTER, J.O. (1979) Cimetidine in the prevention of gastric ulcer relapse. *Postgraduate Medical Journal*, **55**, 393.
- RANDOLPH, W.C., OSBORNE, V.L., WALKENSTEIN, S.S. & INTOCCIA, A.P. (1977) High pressure liquid chromatographic analysis of cimetidine, an histamine H_2 -receptor antagonist, in blood and urine. *Journal of Pharmaceutical Sciences*, **66**, 1148.
- REHFELD, J.F., STADIL, F. & RUBIN, B. (1972) Production and evaluation of antibodies for the radioimmunoassay of gastrin. *Scandinavian Journal of Clinical and Laboratory Investigation*, **30**, 221.
- REHFELD, J.F., STADIL, F., MALMSTRÖM, J. & MIYATA, M. (1975) Gastrin heterogeneity in serum and tissue. In: *Gastrointestinal Hormones*. (Ed. by Thompson, J.C.), p. 43. University of Texas Press, Austin.
- SEWING, K.F., HAGIE, L., IPPOLITI, A.F., ISENBERG, J.I., SAMLOFF, I.M. & STURDEVANT, R.A.L. (1978) Effect of one month treatment with cimetidine on gastric secretion and serum gastrin and pepsinogen levels. *Gastroenterology*, **74**, 376.
- SPENCE, R.W., CELESTIN, L.R., MCCORMICK, D.A., OWENS, C.J. & OLIVER, J.M. (1978a) The effect of long-term treatment with cimetidine on gastric acid secretion and gastric responses in man. In: *Cimetidine Proceedings of an International Symposium on Histamine H_2 -Receptor Antagonists*. (Ed. by Creutzfeldt, W.), p. 116. Excerpta Medica, Amsterdam and Oxford.
- SPENCE, R.W., MCCORMICK, D.A., OLIVER, J.M. & CELESTIN, L.R. (1978b) The effect on serum gastrin of withdrawal of cimetidine after one year's treatment. In: *Cimetidine: Proceedings of the Westminster Hospital Symposium, 1978*. (Ed by Wastell, C. & Lance, P.), p. 153. Churchill Livingstone, Edinburgh, London and New York.